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Three column intermittent simulated moving bed chromatography: 3. Cascade operation for center-cut separations

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ABSTRACT

A general design methodology for chromatographic three fraction separation by application of the three column intermittent simulated moving bed (3C-ISMB) cascade is proposed and experimentally validated by studying the purification of an intermediately retained stereoisomer of nadolol, from an equimolar mixture of its four stereoisomers. The theoretical part shows that the 3C-ISMB cascade can be easily designed by applying Triangle Theory. Moreover, a re-scaling approach for the second stage is proposed so as to account for the fact that the feed flow rates to stage 2 are generally higher as compared to stage 1 due to dilution in the latter. Scaling the columns of the second stage accordingly enables to run both stages under optimal conditions with respect to switching time and step ratio, which is an important advantage as compared to integrated ternary processes. The experimental part starts with studying the linear adsorption behavior of nadolol in heptane/ethanol/DEA on Chiralpak AD for varying ratios of heptane and ethanol. Based on that, a solvent composition of Hept/EtOH/DEA 30/70/0.3 (v/v/v) is selected and the competitive multi-component Langmuir isotherm of the quaternary mixture is determined by frontal analysis. The resulting isotherm parameters are used to design several first stage experiments aiming at removal of the most retained component. The resulting ternary intermediate product is reprocessed in several second stage experiments studying various configurations. Finally, the dilution of the intermediate product with Hept/DEA yielding a solvent composition of Hept/EtOH/DEA 60/40/0.3 (v/v/v) is examined showing that the resulting increase in retention is beneficial for final product purities. Moreover, the reduction in viscosity compensates for the dilution as it enables higher flow rates. Dilution of the intermediate product is hence the best option, yielding highest overall cascade productivity (2.10 $g l^{-1} h^{-1}$) and highest product purity (97.8%) requiring a specific solvent consumption of 12 l/g of product.

1. Introduction

Three column intermittent simulated moving bed (3C-ISMB) chromatography has been introduced and theoretically studied [1] in the first part of this series. In the second part [2] we further demonstrated its potential for binary separations experimentally. This new type of multi-column chromatographic process can be regarded as a modification of the commercialized intermittent simulated moving bed (I-SMB) process [3] or more generally of classical simulated moving bed (SMB) chromatography [4,5].

SMB is a well-established binary separation process being applied at widely varying scales and in different fields of applications that range from the petrochemical [6] and the sugar [7] industry to the fine chemicals and pharmaceutical industry [5]. In the latter area the technology is mainly used for separating enantiomers [5], which not only requires expensive chiral stationary phases (CSPs) but also frequently involves more than two compounds due to the presence of either several stereocenters or of impurities stemming from upstream processes. Both aspects make this kind of separation rather challenging and have triggered two different research interests aiming at (i) the enhancement of productivity for binary separations and thus a more effective use of the stationary phase [1,3,8–13], and (ii) the extension of the SMB technology to enable three fraction separations [14–29]. The former objective has been the subject of parts one and two of this series [1,2], whereas the present contribution exploits those results so as to address the latter. Therefore, the main conclusions of our previous work on the 3C-ISMB technology will be briefly summarized in Section 3.1, whereas the remaining part of this section is focused on the challenges associated with the chromatographic purification of chiral substances involving more than two components, especially compounds with more than one stereocenter, where the target component is neither the most nor the least retained one.

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Most of the earlier studies on three-fraction separations cited above are focused on the process itself and are limited to theoretical process assessment under linear chromatographic conditions. However, the feed concentration is a critical parameter determining productivity and thus economic viability of any chromatographic separation process [30]. Therefore, there is a need for a more holistic approach considering also high feed concentrations, i.e. non-linear chromatographic conditions, which requires a more rigorous evaluation of the system characteristics, especially of the adsorption isotherm. The latter is made particularly difficult for chiral substances involving several stereocenters due to not only the number of components competing for the same adsorption sites, but also due to the fact that the pure single components are usually not available.

In this contribution we therefore address these issues by proposing a general design methodology that consists of comprehensive guidelines ranging from the identification of the chromatographic system, i.e. a proper combination of stationary and mobile phase, over the process design for non-linear chromatographic conditions, to the realization of the preparative isolation of an intermediately retained target stereoisomer. This methodology will be validated experimentally by studying the purification of an intermediately retained stereoisomer of nadolol in heptane/ethanol/DEA on Chiralpak AD. Nadolol is a chiral API with three stereogenic centers, two of them being locked in *cis*-configuration, i.e. it consists of four stereoisomers. To the best of our knowledge this is the first experimental study on the SMB separation of an intermediately eluting stereoisomer under non-linear chromatographic conditions.

The preparative separation will be carried out using a 3C-ISMB cascade, therefore the above mentioned methodology is tailored to this novel process type. However, it is worth mentioning that the same approach is applicable for the SMB cascade [18,22,31] and partly for other SMB based ternary separation processes proposed earlier [14–29], as it will become clearer when discussing our general solution strategy.

2. Design methodology

The design methodology proposed in this work is illustrated in Fig. 1 and will be explained in the following for a generic quaternary mixture of four stereoisomers that are labelled A, B, C, and P where P represents the intermediately retained target component, whereas A and C denote the least and most retained component, respectively, and B can elute either before or after the target component P. In order to be consistent with the following experimental part (Sections 4 and 5), we assume here that the order of retention is given by A-B-P-C.

The selection of the proper combination of CSP and mobile phase (MP) is the starting point of any chromatographic separation process. Given the wealth of commercially available CSPs [32] and the possible combinations thereof with MPs, this first step is anything but trivial. Generally, it requires an extensive and cumbersome screening involving several CSPs and applying different MPs. Guidelines for an efficient screening are available from column manufacturers such as Chiral Technologies and will not be treated here. This step might be further assisted through consulting the relevant open literature or the application guides from column suppliers. In any case, this first step is completed once a combination of CSP and MP is found, that successfully resolves at least components B, P, and C. It is worth mentioning, that the cascade operation offers in principle the flexibility to employ different CSPs with different selectivities in the two stages, however for the sake of simplicity we restrict ourselves in the following to the use of the same CSP for both stages.

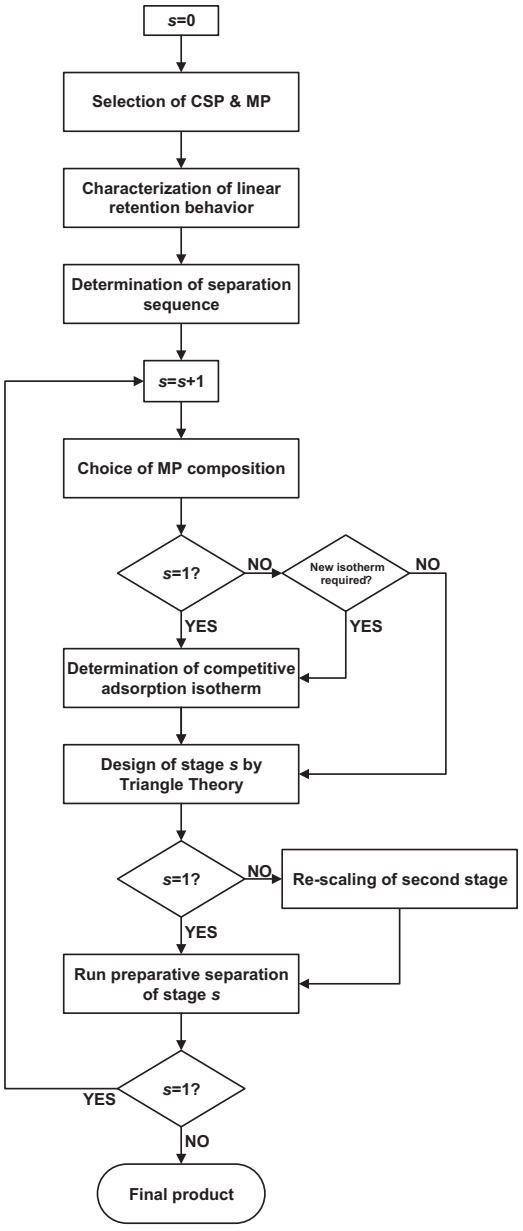

Fig. 1. Overview on the general design methodology proposes in this work (*s* represents the stage number).

In the next step, the retention behavior of the four components under linear conditions for different solvent compositions is studied. It is noted that this step is restricted to the solvent mixture selected in the previous step, i.e. only the ratio of polar and apolar solvent is varied so as to find a good compromise between retention and resolution. More specifically, we aim here at an MP composition yielding Henry's constants in the range between 1 and 5, which as a rule of thumb is a good working range for preparative separations [33]. This step is assisted by applying the Soczewinski equation [34] which relates Henry's constants to solvent composition as further explained in Section 5.1.

Upon completion of step 2 the separation sequence needs to be determined, as for cascades of distillation columns [35]. In other words, it is necessary to decide whether stages 1 and 2 are coupled via the extract (split AB/PC in stage 1) or the raffinate (split ABP/C in stage 1) stream of the first stage. We propose to base this decision on the knowledge of the linear adsorption behavior as described