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Application of an eremomycin-chiral stationary phase for the separation of DL-methionine using simulated moving bed technology

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Abstract

Recently a new chiral stationary phase (CSP) was introduced, based on the immobilization of the macrocyclic glycopeptide eremomycin to epoxy-activated silica. The application of this new CSP to preparative enantioseparation using simulated moving bed (SMB) chromatography will be presented. MeOH–H_2O (0.1 M NaH_2PO_4) = 20/80 (v/v) was used as the mobile phase to separate the enantiomers of methionine. Successful separation was realized providing productivities around 15 $g_{product}/l_{stat}/h$ for both L and D-methionine under nonlinear conditions. In such delicate continuous chromatographic separation processes, besides productivity, the long-term stability of the applied stationary phases is of importance. 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.

Keywords: Eremomycin; Chiral stationary phase; Methionine; Simulated moving bed chromatography; Adsorption isotherms; Stability

1. Introduction

Preparative chromatography has become an accepted tool in pharmaceutical industry for the production of enantiopure drugs and intermediates. An important reason is the achieved and still increasing availability of efficient chiral stationary phases (CSP). Currently macrocyclic glycopeptide antibiotics are increasingly applied to separate enantiomers. They were introduced in 1994 by Armstrong et al. [1] as a new class of chiral selectors. Commercially available macrocyclic glycopetide chiral stationary phases (e.g. chirobiotic V, T, TAG, and R) are based on the following antibiotics as chiral selectors: teicoplanin and teicoplanin aglycone, vancomycin and ristocetin A [2–4]. They contain complex chiral recognition sites providing multiple stereoselective interactions with analytes. They have been successfully applied to various separation modes [2,4]. Recently a new CSP was introduced based on eremomycin as the chiral selector [5]. This new phase has been shown to have a good selectivity with regard to amino acids in analytical and preparative chromatographic applications [6]. It can be prepared by immobilizing the eremomycin to epoxy-activated silica particles under mild conditions [5,7]. This eremomycin CSP was used with methanol–water eluents. It demonstrated a high enantioselectivity for the separation of amino acids, especially aromatic and cyclic imino acids [5]. The retention and separation factors of α-amino acid enantiomers were determined under analytical conditions and the adsorption isotherms of D- and L-methionine were determined to evaluate the potential with respect to preparative separations [6].

Simulated moving bed (SMB) chromatography as an efficient separation process has gained increasing importance in the production of enantiopure drugs and intermediates [8–11]. The advantages of SMB technology are the continuous operating mode, a higher productivity and a lower solvent consumption compared to batch column chromatography [9]. Moreover, nowadays the technology can be easily scaled up. Efficiency and productivity have been in the last years constantly increased due to innovative process models allowing for rigorous optimisation, e.g. [12–15]. For preparative enantioseparation, besides selectivity, the long-term stability of stationary phases is important. SMB performance is governed by the chromatographic process. Consequently, a change of the adsorption behavior of a column

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in time might impair SMB operation. From the perspective of a single column, SMB conditions are characterized by cyclic adsorption and desorption of large amounts of the compounds to be separated. Bechtold et al. measured the column stability under SMB-like conditions by feeding alternating concentrated solution of DL-methionine and pure solvent [16].

In this work, the application of the new eremomycin based CSP to preparative enantioseparation using SMB will be presented. The separation of the methionine enantiomers is used as a model system. Competitive adsorption isotherms of D- and L-methionine were measured up to the solubility limit in the mobile phase by means of a perturbation method. A critical test for the stability is the application in an SMB-unit, where the stationary phase is subject to high sample concentrations and periodically changing operation conditions. The results of the determination of the adsorption isotherms, the evaluation of the stability of the columns and the results of the performed SMB-runs will be presented and discussed.

2. Experimental

2.1. Materials

For this study, eight columns were used: Diaspher-Chirasel-E (BioChemMack S&T, Moscow, Russia); 6 cm × 0.8 cm; particle size: 15 μm. The columns were slurry packed by Knauer (Berlin, Germany).

For analysis, another column was applied: Diaspher-Chirasel-E; 10 cm × 0.46 cm; particle size: 5 μm. The mobile phase was methanol–water (20/80) mixed with 0.1 M NaH_2PO_4 (pH 4.4).

D-, L-, and DL-methionine were purchased from Sigma–Aldrich (Steinheim, Germany). HPLC grade methanol and sodium dihydrogenphosphate (NaH_2PO_4) were supplied by Merck (Darmstadt, Germany). Deionized water was purified using a Milli-Q gradient system (Millipore, Molsheim, France).

2.2. Apparatus

The analysis of the samples and the perturbation experiments were carried out using a HP 1100 liquid chromatography system equipped with a vacuum degasser, a quaternary pump system, an autosampler, a diode array UV detector and the HP-ChemStation software for the data acquisition (Hewlett-Packard, Waldbronn, Germany).

The laboratory-scale SMB unit ICLC 1610 is from Prochrom (now Novasep, Pompey, France). Scheme of the SMB-unit is shown in Fig. 1. Five 16-port valves (Valco, Houston, TX, USA) are used inside the unit. The continuous operation the SMB process is achieved by 16 ports switching valves connected with the two inlet streams and two outlet steams in the required manner. In addition to the valve unit the system is equipped with four HP 1050 pumps (Agilent Technologies, Palo Alto, CA, USA). Two Dynamax UV-1 detectors from Rainin (Woburn, MA, USA) monitor the outlets of raffinate and extract. An injection valve was positioned in the flow path prior to column 1. The SMB unit is controlled by regulating the switching time, and the setting of the five valves with the SIMATEC 7 software (Siemens,, Munich, Germany).

2.3. Procedures

Competitive adsorption isotherms of D- and L-methionine were measured up to the solubility limit in the mobile phase by means of a perturbation method. The principle of the perturbation method is based on a stepwise saturation of the column with different known feed concentrations. After reaching equilibrium small samples possessing a different concentration are injected and the corresponding retention times are measured. They provide information about the local isotherm slopes. Since the method depends only on the analysis of times no detector calibration is necessary. Details on that method are given elsewhere [17]. For the perturbation experiments one column as

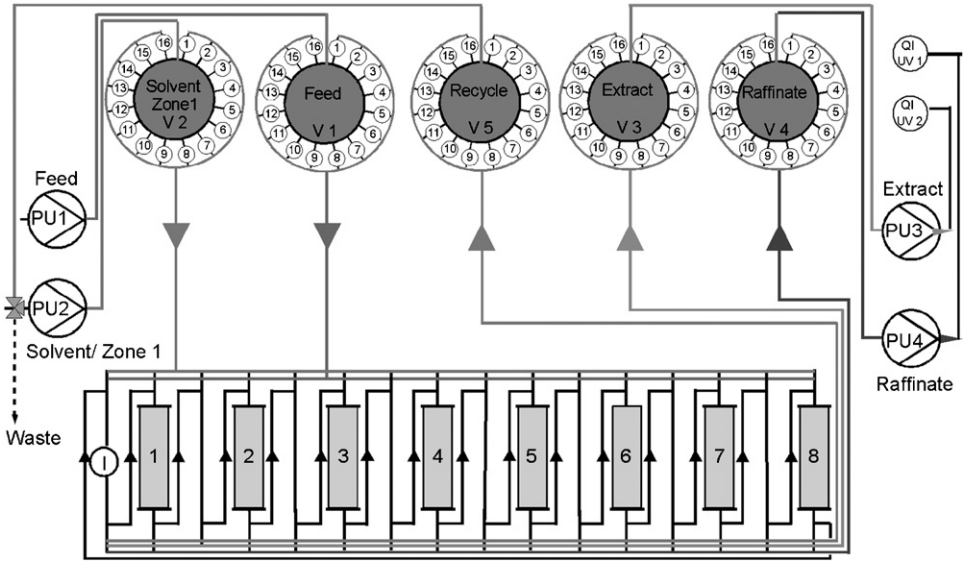

Fig. 1. Scheme of SMB setup. V: switching valve (for maximum 16 columns); PU: pump; I: injection valve.