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Continuous chromatographic separation of a baclofen precursor (*N*-Boc-4-[*p*-chloro-phenyl]-2-pyrrolidone) in a simulated moving bed using a polysaccharide carbamate as chiral stationary phase

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Abstract

Liquid chromatography is known as one of the most flexible, efficient and cost-effective methods to resolve racemic mixture in order to attend the growing demand of the pharmaceutical industry for pure enantiomeric compounds. Cellulose tris(3,5-dimethylphenylcarbamate) is frequently used as a stationary phase for enantiomeric separations because of its attractive properties, including high enantioselectivity, high loading capacity and good mechanical stability. In this study, we investigated the usefulness of cellulose tris(3,5-dimethylphenylcarbamate) as the stationary phase and of ethanol and hexane mixtures as the mobile phases for the chromatographic separation of potential pharmaceutical intermediates. Using adsorption equilibrium data, we determined the optimal operational conditions for the separation of the *N*-Boc-4-[*p*-chloro-phenyl]-2-pyrrolidone enantiomers – a baclofen precursor – in a semi-preparative scale simulated moving bed unit. This unit was used to obtain high purity enantiomers on a scale of 1 g/day. The outlet streams were analyzed by an on-line system that consisted of a UV–vis spectrophotometric unit, a polarimeter, and HPLC. Enantiomeric purities of up to 97% were obtained for the raffinate stream and up to 90% for the extract stream.

Keywords: SMB chromatography; Enantiomer separation; Preparative chromatography; (*N*-Boc-4-[*p*-chloro-phenyl]-2-pyrrolidone); Cellulose tris(3,5-dimethylphenylcarbamate)

1. Introduction

The improvement of solute selectivity is a general theme in the field of separation processes. The power of modern synthetic chemistry, in conjunction with technologies in separation sciences, can be used to develop new agents and equipment with enhanced capacity for selective separation. Such associations can help meeting the growing demand of the pharmaceutical industry for efficient and cost-effective methods for purifying optical isomers [1]. Continuous preparative chromatography has been employed as an important process for the chemical manufacture of several chiral compounds [2].

Simulated moving bed (SMB) is a large-scale version of traditional high-performance liquid chromatography (HPLC), but unlike normal HPLC, SMB operates continuously, without loss of the enantiomeric purity in outlet streams. This process consists of simulating the countercurrent movement of the adsorbent bed by switching the positions of inlet and outlet streams to produce two outlet streams, one of which is rich in the more adsorbed component (extract stream), while the other is rich in the less adsorbed component (raffinate stream). This procedure is appropriate for binary separations such as required for racemates. The SMB system has been used to separate components from racemic mixtures [3], since it can provide two enantiomers of a chiral molecule with sufficiently high purity and quantities for clinical tests or even production stages. The variety of chiral selectors used as stationary phase and the vast number of racemic mixtures produced by the pharmaceutical industry make this technique a powerful tool and provide a stimulating

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and challenging area of research for both laboratory scale studies and production plant designs.

The aim of this work was to determine basic chromatographic data and to use a SMB laboratory scale unit to separate the baclofen precursor *N*-Boc-4-[*p*-chloro-phenyl]-2-pyrrolidone from the racemic mixtures of this chiral compound. This pharmaceutical intermediate served as a model molecule for separation in this system and was purified using cellulose tris(3,5-dimethylphenylcarbamate) as the stationary phase and ethanol and hexane mixtures as mobile phases.

2. Materials and methods

2.1. Racemic mixture used for separation: N-Boc-4-[p-chloro-phenyl]-2-pyrrolidone

The racemic mixture resolved in this work was synthesized according to ref. [4] in three steps starting from *N*-Boc-3-pyrroline with overall yields in the range of 65–80%. The first step consisted of Heck arylation of *N*-Boc-3-pyrroline with an aryldiazonium salt to form an intermediate lactamol, which was used in the next step without further purification. The next step involved the oxidation of the lactamol by pyridine chlorochromate (PCC) to provide the corresponding lactam in good quantity. This compound is a precursor of baclofen (a simple acidic hydrolysis gives baclofen in high quantities), which is used as a muscle relaxant. The structure of *N*-Boc-4-[*p*-chloro-phenyl]-2-pyrrolidone is shown in Fig. 1.

2.2. Stationary and mobile phases used for separation

N-Boc-4-[*p*-chloro-phenyl]-2-pyrrolidone has chiral properties; it was separated using columns packed with cellulose tris(3,5-dimethylphenylcarbamate) supported on a matrix of aminopropylated silica (Luna NH_2) with an average particle diameter of 10 μm and average pore diameter of 100 Å. The chiral stationary phase was prepared as previously reported [5–8].

A semi-preparative column (0.8 cm i.d. × 15 cm length) was packed with the prepared stationary phase under a pressure of 517 bar. The mobile phase used was a mixture of hexane and isopropanol (80:20, v/v). The average mass of chiral stationary phase in each column was 7.5 g.

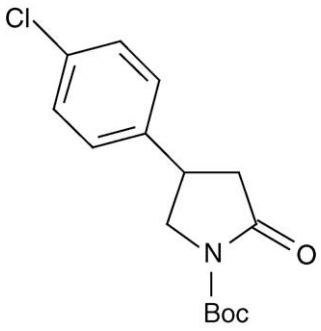

Fig. 1. Molecular structure of *N*-Boc-4-[*p*-chloro-phenyl]-2-pyrrolidone.

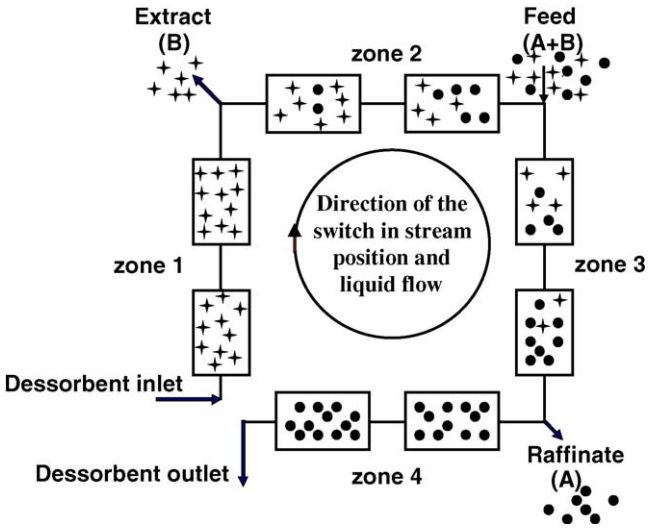

Fig. 2. Basic scheme of the SMB laboratory-scale unit.

2.3. Description of the simulated moving bed (SMB) chromatographic unit

The laboratory-scale SMB unit consisted of eight stainless steel columns (0.8 cm × 15 cm) distributed in four pairs of two columns each (Fig. 2). The desorbent was recycled outside the series of columns by using a multiposition valve instead of a solvent reflux pump. Other four multiposition valves changed the positions of the feed, desorbent inlet, raffinate and extract outlets at preset switch times. These valves were connected to four semi-preparative liquid chromatographic pumps (Shimadzu LC-6AD). Fig. 3 provides some details of the complete setup. The multiposition valves (Valco Instruments Co.) were electrically controlled and linked to a computer by a data-acquisition board. Each valve operated the unit automatically changing positions at pre-determined time intervals. These valves were controlled by a program developed with Labview® software.

The unit also contained a sampling valve connected to one of the columns of the series that permitted the collection of internal samples. Analysis of these samples enabled determination of the internal concentration profiles of the (−)*N*-Boc-4-[*p*-chloro-phenyl]-2-pyrrolidone and (+)*N*-Boc-4-[*p*-chloro-phenyl]-2-pyrrolidone and reflected the dynamics of the separation within the columns. A Shimadzu DGU-14A membrane degasser was used to prevent air bubbles in the system.

2.4. Analytical system of the SMB unit

Purities of the raffinate and the extract streams were continuously monitored to determine the efficiency of the separation. The criteria used to assess the efficiency of the separation were that the raffinate should have the highest possible purity for the less adsorbed component, (−)*N*-Boc-4-[*p*-chloro-phenyl]-2-pyrrolidone, whereas the extract should have the highest purity of (+)*N*-Boc-4-[*p*-chloro-phenyl]-2-pyrrolidone, the more adsorbed component. Although both enantiomers were desirable, the less adsorbed enantiomer was the more valuable