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Chiral separation of β-blocker drug (nadolol) by five-zone simulated moving bed chromatography

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Abstract

Nadolol, a β-blocker drug used in the management of hypertension and angina pectoris, has three chiral centers and is currently marketed as an equal mixture of four stereoisomers. Resolution of three of the four stereoisomers of nadolol was obtained previously by HPLC, with a complete separation of the most active enantiomer (RSR)-nadolol, on a column packed with perphenyl carbamoylated β-cyclodextrin (β-CD) immobilized onto silica gel.

Continuous separation of enantiomer (RSR)-nadolol from its racemate (which is a ternary mixture in the chromatographic system of this study) in both 2-raffinate and 2-extract configuration of five-zone SMB was studied. Same experimental setup was applied to both configurations by modifying SMB controlling program accordingly. Separation performances of the five-zone SMB were investigated for both 2-raffinate and 2-extract configurations and same safety factors were applied to investigate the effect of m_3–m_2 (or m_4–m_3) on the separation performance systematically. The desired enantiomer of nadolol can be produced with a high purity and yield in 2-raffinate configuration compared with that in 2-extract configuration.

Keywords: Chiral separation; Nadolol; 5-zone simulated moving bed chromatography; Ternary separation; β-cyclodextrin

1. Introduction

Chirality has been a major concern in the pharmaceutical industries. Nowadays more research efforts have been concentrated on the production of optically pure products due to increasing demand that such drugs are administered in optically pure form (Decamp, 1989; Rekoske, 2001). Nadolol, 5-{3-[(1,1-dimethylethyl) amino]-2-hydroxypropoxy}-1,2,3,4-tetrahydro-cis-2, 3-naphthalenediol is a β-blocker drug widely used in the management of hypertension and angina pectoris. Its chemical structure has three stereogenic centers which allows for eight possible stereoisomers. However, the two hydroxyl substituents on the cyclohexane ring are fixed in the cis-configuration which precludes four stereoisomers. Nadolol is currently marketed as an equal mixture of four stereoisomers, designated as diastereomers of "racemate A" and "racemate B" (for the molecular structures, refer to Wang and Ching, 2002). Racemate A is a mixture of the most active stereoisomer I ((RSR)-nadolol) and its enantiomer II ((SRS)-nadolol) in 1:1 molar ratio, whereas racemate B is a mixture of stereoisomer III ((RRS)-nadolol) and its enantiomer IV ((SSR)-nadolol) also in 1:1 molar ratio. For a safer and more effective use, it is better to separate the enantiomer (RSR)-nadolol before use.

Simulated moving bed (SMB) process has been extensively applied to the separation of chiral drugs and intermediates (Lehoucq and Verheve, 2000; Francotte et al., 1998; Pais et al., 1997; Pedeferri et al., 1999) over the last decade. Due to continuous countercurrent contact between liquid and solid phases, SMB process allows the decrease of desorbent requirement and the improvement of productivity per unit time and unit mass of stationary phase. Furthermore, SMB

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process is believed to be able to achieve high-purity separation performance even when the resolution exhibited by an individual column is not efficient for a batch preparative separation, which is often encountered in chiral separations.

Although having the advantages of low solvent consumption, high-purity products and high productivity, classical four-zone SMB is only capable of separating binary mixtures or dividing multi-component mixtures into strong adsorbing and weak adsorbing fractions. For a ternary separation, the ternary mixture can be separated into their components by operating two SMBs in a row, which can be either separated or combined in a single device. Other concepts of keeping the four zones either by alternating two different adsorbents or having a variation of the working flow rates with respect to time within a switching period were also proposed (Kearney and Hieb, 1992). Wooley et al. investigated a nine-zone system for glucose–xylose–sulfuric acid–acetic acid separations (Wooley et al., 1998). Five-zone SMB with a third fraction withdrawn from the system besides products of extract and raffinate was also discussed (Nicoud, 1999; Beste and Arlt, 2001; Nicolaos et al., 2003). Recently, a single cascade SMB system was investigated for ternary separation, which is especially suitable for system with little amount of the most strongly adsorbed component and a significant amount of the middle component (Kim et al., 2003). A five-zone SMB system with different strength solvents in different zones was also proposed for ternary separation of biomolecules (Abel et al., 2003).

For the β-blocker drug nadolol, resolution of three of its four stereoisomers was obtained by HPLC in a previous study (Wang and Ching, 2002). A complete separation of the most active enantiomer (RSR)-nadolol was achieved on a column packed with perphenyl carbamoylated β-cyclodextrin (β-CD) immobilized onto silica gel. In this study, separation performance of the ternary mixture of nadolol by the five-zone SMB process was investigated. The study is consistent with the growing demands of multi-component multi-fraction separations when the target drugs have more than one chiral centre.

2. Five-zone SMB separation of ternary mixture

We consider a ternary mixture of component A, B and C and assume that component C is the least retained one, component B is the middle retained one and component A is the most retained one such that $K_A > K_B > K_C$. Components C, B and A correspond to the first (component 1), second (component 2) and third eluted component (component 3) in chromatographic separation of the ternary mixture, respectively. For a better understanding, five-zone SMB can be regarded as a modification of conventional four-zone SMB, with a side stream introduced at the point of highest concentration of the middle component B. In particular, the introduction of the side-stream in Section 2 would result in the division of that section. The separator would then have five sections

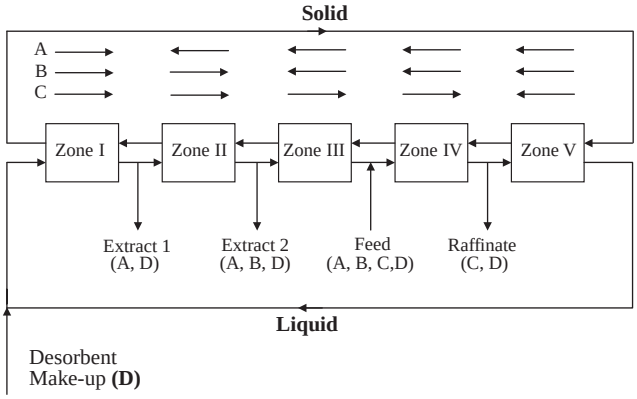

Fig. 1. Liquid and solid streams involved in a ternary TCC process (2-extract configuration).

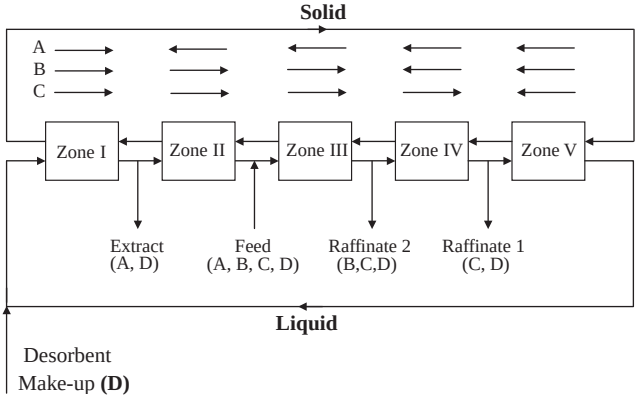

Fig. 2. Liquid and solid streams involved in a ternary TCC process (2-raffinate configuration).

in total and two extract streams, with the feed located between Sections 3 and 4 (see Fig. 1). Similarly, positioning the side-stream in the raffinate region would create the separator with two raffinate streams and a feed located between Sections 2 and 3 (see Fig. 2). For classical four-zone SMB processing a multi-component mixture of M compounds, it is possible to define a KEY component as follows: all components going from 1 to KEY are produced in the raffinate and the remaining compounds going from KEY+1 to M are produced in the extract (Mazzotti et al., 1994). Similarly, for a five-zone SMB separating a ternary mixture, the compounds 1–3 can be produced either in raffinate, Extracts 1 and 2 streams for KEY = 1, or in raffinates 1, 2 and extract streams for KEY = 2. The two configurations are designated as 2-raffinate and 2-extract five-zone SMB, respectively and the side stream is called extract 2 and raffinate 2 for the two configurations, respectively.

For 2-raffinate configuration SMB, desired separation is achieved if each component migrates to its corresponding product outlet, as indicated by the arrows in Fig. 2. However, it should be noted that, although the amount of component C in raffinate 2 stream can be minimized, some C in this stream is inevitable since component C must pass through that point