

Chiral Separation of Non-Steroidal Anti-Inflammatory Drugs by Preparative and Simulated Moving Bed Chromatography

António E. Ribeiro^{a,*}, Pedro Sá Gomes^b, Luís S. Pais^a and Alírio E. Rodrigues^b

^{a,*}Laboratory of Separation and Reaction Engineering, Polytechnic Institute of Bragança, Campus de Santa Apolónia, Apartado 1134, 5301-857 Bragança, Portugal

^bLaboratory of Separation and Reaction Engineering, Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias s/n, 4200-465 Porto, Portugal

*aribeiro@ipb.pt; Tel: +351 273 303 125

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Abstract: The work presents modelling, simulation and experimental results for the chiral separation of non-steroidal anti-inflammatory drugs, particularly, the optimization of mobile phase composition under preparative and simulated moving bed chromatography. The experimental separation of two chiral systems (ketoprofen and flurbiprofen enantiomers) will be presented to show how compounds of the same family can lead to different solutions.

Over the last decade, an important improvement on the performance of Simulated Moving Bed (SMB) technology has been noticed, mostly due to academic community contributions, exploring and developing new and non conventional and more efficient modes of operation (Sá Gomes *et al.*, 2006; Seidel-Morgenstern *et al.*, 2008; Rajendran *et al.*, 2009). Its practical advantages over other classical techniques allowed SMB technology to become an attractive method for large scale process separation in several industry fields such as biotechnology, pharmaceuticals and fine chemical products.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), are frequently prescribed worldwide in relieve of pain and, mainly, in the treatment of several forms of inflammation associated with articular diseases such as the rheumatoid arthritis. Regardless the considerable evidence that (-)-R and (+)-S enantiomers have important and different therapeutic actions, the narrow international legislation concerning chiral drugs safety still allows its commercialization in the form of racemic mixtures.

The optimization of the mobile phase composition is known as a key aspect when dealing with preparative scale separations, as is the case of SMB chiral chromatography. However, today, there are still very few published studies concerning this paramount issue, and the main goal of this study is to bring more knowledge into this field.

In this work, it will be presented a complete study on how mobile phase composition can drastically affect the performance on SMB chiral separations. To clearly demonstrate this completion, a complete study of the chiral separation of ketoprofen and flurbiprofen enantiomers (two important NSAIDs) by SMB chromatography is performed. The adopted methodology will follow the author's findings of previous published works (Ribeiro *et al.*, 2008 and 2009). First, competitive adsorption isotherms, elution and frontal chromatography experiments using different mobile phase compositions are compared. Then, modelling and simulation tools are used to predict the adsorption behaviour of fixed-bed chromatography and the performance of the real SMB separation process (using preparative conditions, i.e., very high concentrations). Finally, experimental separation of ketoprofen and flurbiprofen enantiomers is carried out by SMB chromatography, using the 6-column FlexSMB-LSRE[®] unit (Sá Gomes *et al.*, 2010). The experimental results will clearly stress that a proper selection of the mobile phase composition is crucial for the success of a preparative chiral separation performance. Further, results will also demonstrate that there are no predictive general rules for the optimization of mobile phase composition in a preparative point of view, since two drugs of the same family can lead to very different solutions.

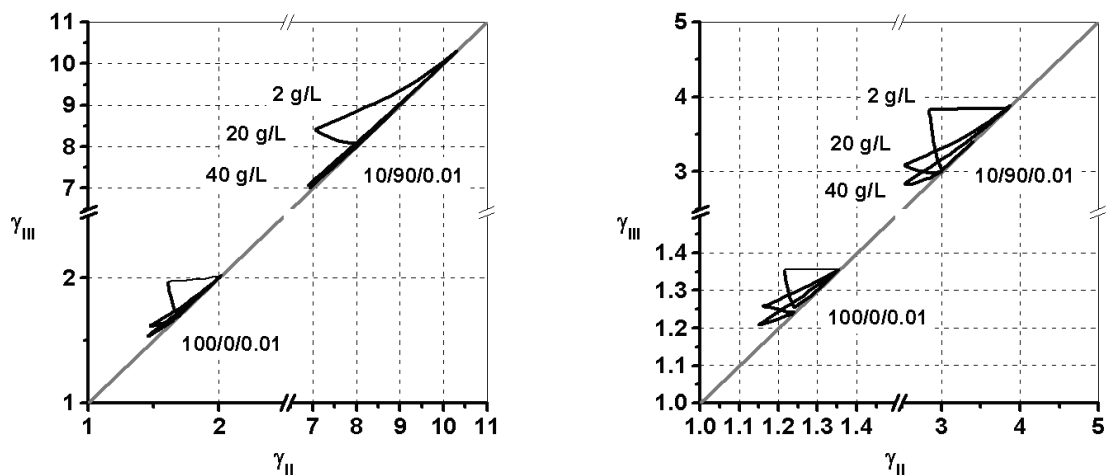


Figure 1. SMB separation regions for the two mobile phase compositions (10/90/0.01 and 100/0/0.01 ethanol/n-hexane/TFA) and three different racemic feed concentrations (2, 20 and 40 g/L). Ketoprofen enantiomers (left) and flurbiprofen (right).

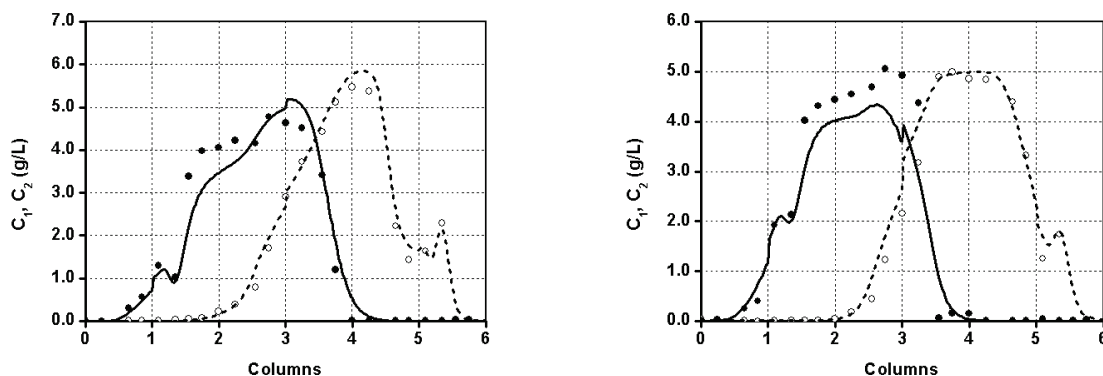


Figure 2. Experimental and simulated internal concentration profiles at cyclic steady state. Dashed line and open circles for the less retained enantiomer; solid line and closed circles for the more retained enantiomer. Racemic feed concentration of 20 g/L. Ketoprofen enantiomers (left) and flurbiprofen (right).

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