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Book of Extended Abstracts

Edited by:
João Araújo Pereira Coutinho
Carlos Manuel Silva
Inês Portugal
Ana Barros-Timmons
Anabela Aguiar Valente
Dmitry Victorovitch Evtyugin
Mara Guadalupe Freire
Pedro Jorge Carvalho

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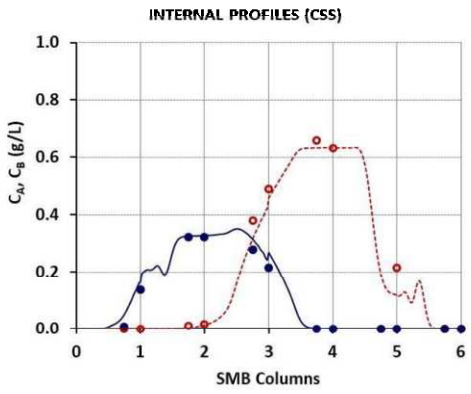
Separation of nadolol racemates by high pH reversed-phase simulated moving bed chromatography

R. Arafah[1,2], A. Ribeiro[1,2], A. Rodrigues[2], L. Pais,[1,2,*]

[1]Centro de Investigação de Montanha (CIMO), Polytechnic Institute of Bragança, Campus de Santa Apolónia, Apartado 1134, 5301-857 Bragança, Portugal; [2]Laboratory of Separation and Reaction Engineering, Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias s/n, 4200-465 Porto, Portugal.

*pais@ipb.pt



Nadolol is a pharmaceutical drug marketed as a mixture of four stereoisomers, used to treat cardiovascular diseases. This drug is a mixture of two pairs of racemates, therefore, its complete separation represents a challenging task. Recently, our research group reported the pseudo-binary separation of nadolol by SMB chromatography using both coated Chiralpak AD and Chiralpak IA immobilized chiral stationary phases. In this work, we present an alternative strategy, implementing a first achiral separation step, by using C18 columns to perform the separation of the two pairs of nadolol racemates under reversed-phase mode. Extensive experimental and simulation results will be presented including solvent screening, measurement of equilibrium and kinetic data, and both fixed-bed and SMB preparative separations. Extensive experimental and simulation results will be presented, including solvent screening, measurement of equilibrium adsorption isotherms, breakthrough measurements, and SMB (FlexSMB-LSRE unit) experimental preparative separation using C18 columns.

Introduction

The main objective of this work is to improve the recent findings on the pseudo-binary separation of nadolol stereoisomers and to achieve the real multicomponent separation of all its four components. This introduces much more deep and new challenges involving optimization of the packing to be used, the solvent composition, and the strategy for defining the different separation steps and its sequences.

Different separation strategies can be designed and optimized, enlarging the packing materials possibilities, from fully chiral (Chiralpak) to achiral (C18) – chiral (Chiralpak) separation combinations and, so, the used of both normal and reversed phase chromatography. For each step, the optimization of the solvent composition will be carried out, through the use of pure alcohol, alcohol-hydrocarbon and alcohol-water mixtures, all with a basic modifier (diethylamine), taking into account the strong basic nature of the nadolol stereoisomers. The separation technique to be used will also be tested, including fixed-bed, SMB and JO chromatography. The different alternatives will be evaluated in terms of the real capacity to achieve complete separation of all the four nadolol stereoisomers and in terms of system productivity and solvent consumption.

Considering the previous tasks, both modeling-simulation and experimental tools will be fully used, namely in what concerns the knowledge of the equilibrium adsorption isotherms, kinetic data (axial dispersion and resistance to mass transfer), and the prediction of fixed-bed, SMB and JO operation. This chemical engineering approach will allow the deep knowledge of all the separation processes and its optimization at preparative scale.

At the end is expected the clear definition of the best separation strategy for the complete separation of nadolol stereoisomers and the experimental availability of all the four pure stereoisomers for new pharmaceutical and therapeutical tests.

Materials and methods

The mixture of the four nadolol stereoisomers of nadolol and 1,2,3-tri-tert-butylbenzene, used as the non-retained compound, were both obtained from Sigma-Aldrich (Schnelldorf, Germany). The basic modifier diethylamine (DEA), methanol (M), acetonitrile (ACN), all HPLC grade solvents, were obtained from Fluka (Buchs, Switzerland). All reagents and solvents were used without further purification. Different types of chromatographic columns were used. One chiral column, named Chiralpak IA, and one achiral column, named Waters XBridge C18 column, both with analytical dimensions (4.6mm ID x 250mm L) and particle size diameter of 5 µm. Seven achiral Waters XBridge columns with the preparative dimensions (19mm ID x 100mm L) and a particle size diameter of 10 µm, named as "SMB columns".

The preliminary screening of the solvent composition and the analytical pulses of nadolol were performed using a Knauer analytical HPLC system equipped with one Smartline 1050 pump with a 10 mL pump head, a Smartline UV detector 2520 set at a 270 nm and a manual Rheodyne injection valve with a 20 µL loop. A constant flow-rate of 1 mL/min was used with all the analytical columns.

The loading experiments, the measurements of the equilibrium adsorption isotherms and the breakthroughs experiments were carried out using a preparative Knauer HPLC system equipped with a Smartline UV detector 2520 set. at 270 nm wavelength, two Smartline 1050 pumps with 50 mL pump heads, a manual injection valve and two different loops (100 and 1000 µL). A constant flow-rate of 5 mL/min was used.

The pseudo-binary SMB separation of nadolol stereoisomers were performed on a laboratory-scale SMB unit. This unit was completely built on the LSRE group, Faculty of Engineering, University of Porto, and is designated as "FlexSMB-LSRE". The SMB unit was operated using a [1-2-2-1] columns configuration.

Results

An extensive set of experimental and simulation results will be presented. Results will include the identification of the stereoisomers present in both nadolol racemates by means of using UV and polarimeter detectors in series.

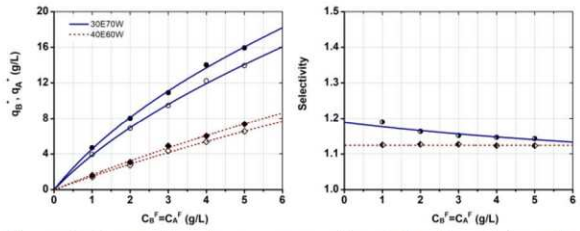


Figure 1. Comparison between experimental and model results on the adsorption equilibrium isotherms for nadolol stereoisomers using 30%ethanol/70%water and 40%ethanol/60%water solvent compositions. Left figure, the multicomponent adsorption equilibrium isotherms and its fitting to a linear + Langmuir competitive model (solid line, 30E70W) and Langmuir model (dashed line, 40E60W); right figure, the experimental selectivity (points) and its fitting using the selected isotherm models (lines), between the racemate A and the racemate B, as a function of their feed concentrations.

Then a complete methodology, developed during the last years by our group used and explained to scale-up the separation process from analytical to preparative chromatography [1-3].

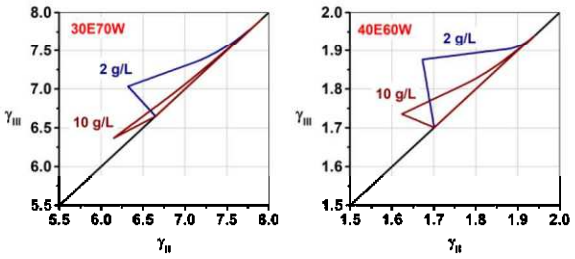


Figure 2. SMB complete separation regions for the pseudo-binary separation of racemate B (stereoisomers 2 and 3) from racemate A (stereoisomers 1 and 4) using XBridge C18 stationary phase using 30%ethanol/70%water (left plot) and 40%ethanol/60%water (right plot) solvent compositions and for total feed concentrations of 2 g/L and 10 g/L.

This large set of results will include the screening of solvent composition using an achiral adsorbent and measurements of the column efficiency; the experimental determination of the equilibrium adsorption isotherms and the fitting to an appropriate equilibrium adsorption model (See Fig. 1); then, the model validation by means of breakthroughs measurements with the estimation of the Peclet and mass transfer resistance coefficient; the prediction of the separation regions (See Fig. 2) and the main performance parameters, such as the productivity and solvent consumption (See Fig. 3); finally, the final results of the experimental separation of the nadolol racemates by simulated moving bed chromatography.

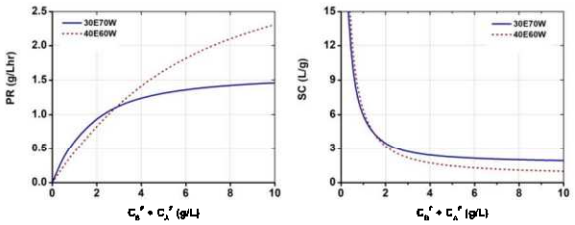


Figure 3. Prediction of SMB: (left) productivity and (right) solvent consumption for the two solvent compositions, as a function of the feed concentration (mixture of the four stereoisomers). Solid line for the 40E60W and dashed line for the 30E70W composition.

Conclusions

The results recently obtained by our research team for this topic, clearly supports the capacity to enhance the knowledge on the chromatographic separation of chiral pharmaceuticals using preparative and SMB chromatography. In this communication we will introduce original and innovative challenges through the real separation of multicomponent (quaternary) chiral mixtures which will represent an important step forward for the pharmaceutical industry.

Acknowledgements

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