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Book of Abstracts

4th Symposium on Chemical and Biological Engineering

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Editors:
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Complete separation of the quaternary mixture of nadolol stereoisomers using preparative and simulated moving bed chromatography

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Abstract

The separation and purification of high added value products by liquid chromatography is a very popular technique. The development of more stable and efficient stationary phases, together with the design of innovative and more flexible separation processes, enhanced the use of chromatographic processes, particularly at preparative and industrial scales through fixedbed and simulated moving bed (SMB) technologies. Fixed-bed and SMB techniques are more and more used in the separation of a wide range of products for the pharmaceutical, fine chemistry, biotechnology and food industries. In this context, one of the actual main challenges concerns the design and optimization of these chromatographic processes for challenging multicomponent separations. This includes the development of new and innovative chromatographic processes, combining different design strategies and modes of operation, with different types of stationary and mobile phases.

The design and optimization of a chiral separation process for a specific chiral binary or pseudo-binary mixture is based on a careful selection of the proper combination between the chiral stationary phase and the mobile phase composition. When considering multicomponent separations, the complexity deeply increases by the introducing of multi-step separation sequences (or a much more complex multi-region separation process). This can be done by opening the possibility to combine chiral and achiral stationary phases (when in presence of stereoisomers instead of just one pair of enantiomers) and to combine different separation techniques such as the fixed-bed and SMB related processes.

Nadolol is a worldwide prescribed pharmaceutical drug for the relieve of several cardiovascular diseases and represents a very interesting case-study of multicomponent chiral separation since it is composed by four stereoisomers, being two pairs of enantiomers. In this way, it introduces the possibility of alternative strategies, using different kind of preparative separation sequences and techniques, and also the use of different packings (chiral and achiral stationary phases), and the corresponding mobile phase optimization at both normal and reversed-phase modes.

The design of the complete preparative separation of nadolol stereoisomers asks for a global experimental and simulation methodology considering both the characterization and optimization of each separation step and its sequences to achieve the four nadolol components pure. New strategies using combinations of achiral and chiral stationary phases and sequences of different separation techniques will be presented. Extensive experimental and simulation results for the complete separation, using fixed-bed (Azura preparative HPLC) and SMB (LSRE-

FlexSMB) pilot units, of all the four nadolol stereoisomers using Chiralpak IA (chiral) and different Waters C18 (achiral) stationary phases 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. Then, a complete methodology developed during the last years by our group will be explained and applied to scale-up the separation process from analytical to preparative scales [1-4].

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

Author Keywords. SMB, chromatography, Nadalol, stereoisomers.

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