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## Separation of nadolol stereoisomers using different simulated moving bed strategies

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Nadolol is a pharmaceutical drug marketed as a mixture of four stereoisomers, used to treat cardiovascular diseases. However, its prescription is also related with some severe risks such as heart failure. It is well known that pure enantiomer separation is important to control chiral drugs safety. Recently, our research group reported the pseudo-binary separation of nadolol by simulated moving bed (SMB) technology using both coated Chiralpak AD and immobilized Chiralpak IA chiral stationary phases (CSP) [1,2].

The introduction of a wide range of new and more powerful preparative stationary phases allied to the development of new and more versatile strategies and modes of SMB operation are now a reality. Several configurations have been proposed in order to extend the SMB technology to the separation of multicomponent mixtures by using a cascade of SMBs in series or other complex SMB related techniques like multi-zone SMB, intermittent SMB and JO processes. The JO technology allows the separation of ternary mixtures through a cyclic process constituted by two discrete steps [3,4].

In this work, different strategies for the complete separation of the nadolol quaternary mixture are presented, by using different solvent compositions, CSP and SMB related techniques. Experimental and simulation results will be presented including: (i) The use of Chiralpak IA CSP that, comparing to Chiralpak AD, allows the use of a wider range of solvents and therefore better separation performances; (ii) The use of the JO process to achieve a final ternary separation, applied to the mixture of the three stereoisomers co-eluted in the raffinate in the previous separation; and (iii) The separation of the two pairs of nadolol enantiomers using an achiral C18 material, followed by two parallel SMB binary chiral enantioseparation steps.

The application of these different approaches represents possible SMB strategies for the complete separation of the quaternary nadolol chiral mixture and will be compared in terms of system productivity and solvent consumption.

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