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Multicolumn based liquid chromatography processes for the separation of nadolol racemates

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A few decades passed since the pharmaceutical industry realized the need to produce chiral drugs with reduced severe side-effects. To overcome this issue, the international agencies for drug safety become a real driving force, pushing more and more the industry towards the commercialization of drugs based on pure enantiomers. Traditionally, enantiomerically pure drugs are still produced in large-scale by organic asymmetric synthesis. However, it is also accepted that, in several cases, it is a too much time consuming production path. The direct resolution of racemic compounds, using multicolumn or fixed-bed liquid chromatography technologies, are nowadays, recognized at an industrial scale has a true alternative. The use of such technologies, like simulated moving bed (SMB) chromatography allows both high yields and purities of both enantiomers present in the racemic chiral compound. Also, these techniques can be applied to a wide range of racemic mixtures, since different stationary phases for enantiomer separation are now available. 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 [1,2]. In this work, it is proposed an alternative strategy, implementing a first achiral separation step, to be followed by two subsequent parallel chiral separation steps [3]. In this first achiral step, C18 columns are used to perform the separation of the two pairs of nadolol enantiomers ("racemate A" from "racemate B") under reversed-phase mode. After this preliminary achiral separation step, two parallel SMB runs must be carried out using a chiral stationary phase to achieve the complete separation of all the four nadolol stereoisomers. 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.

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