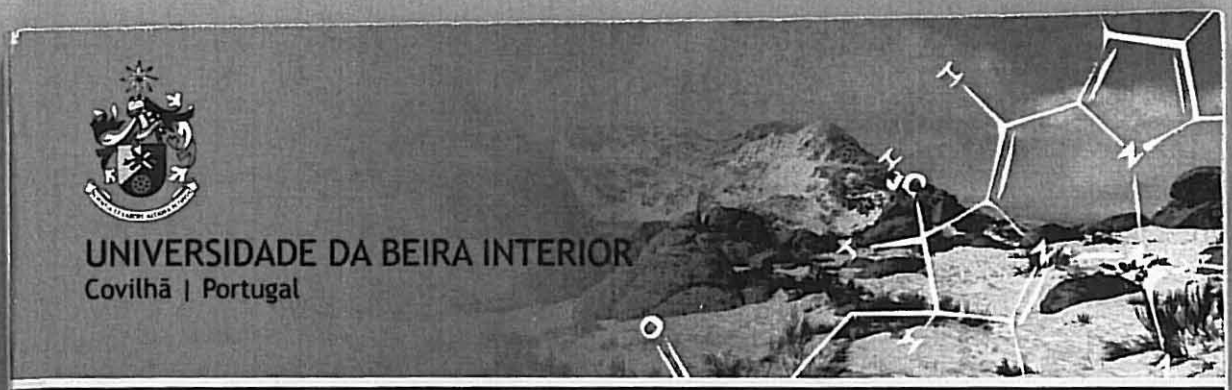

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LIVRO DE RESUMOS

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CO.25. Multicomponent Chiral Separations by Analytical and Preparative Liquid Chromatography

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Nadolol is a non-selective beta-adrenergic receptor antagonist (β-blocker) pharmaceutical drug, widely used in the treatment of cardiovascular system diseases, such as hypertension, ischemic heart disease (angina pectoris), congestive heart failure and certain arrhythmias [1]. Its chemical structure has three stereogenic centers which allows for eight possible stereoisomers. However, the two hydroxyl substituents on the cyclohexane ring are fixed in the *cis*-configuration which precludes four stereoisomers [2]. Regardless the considerable evidence that it is important to characterize the stereochemical components when describing the pharmacodynamics and pharmokinetics of a racemic drug, the narrow international legislation concerning chiral drugs safety still allows the nadolol commercialization in the form of a racemic mixture of four stereoisomers (see Fig. 1).

The separation of nadolol stereoisomers on CHIRALPAK® AD at both analytical and preparative scales was recently reported by Ribeiro et al. [3]. CHIRALPAK® AD is, nowadays, the most used commercially available CSP. It is an amylose-based CSP and is produced by physical coating of the chiral polymer on a matrix. However, due to their coated nature, this CSP can only be used with a limited range of solvents such as the polar solvents (e.g. acetonitrile, alcohols) or non-polar solvents (e.g. alkanes) in combination with some polar components as modifiers (mainly alcohols). Immobilization of a polysaccharide-derivative on the support is an evolutionary strategy to make a CSP compatible with the whole range of organic solvents, which will consequently extend its application scope. CHIRALPAK® IA is a CSP containing amylose 3,5-dimethylphenylcarbamate immobilized onto silica gel [4].
This work will present a complete methodology concerning experimental, modelling and simulation results. Both the CHIRALPAK® AD and CHIRALPAK® IA CSP will be evaluated. The selection of the proper CSP/solvent combination for preparative operation will be fully study taking into account the screening

strategy proposed by Zhang et al. [5]. Additional results include the measurement of nadolol stereoisomers solubilities, equilibrium adsorption data and fixed bed (breakthroughs) experiments. The complete screening of CSP/solvent combination will lead to the choice of the better solutions for the separation of nadolol stereoisomers, considering the target component or components to be obtained. Simulation and experimental results will be presented for the multicomponent separation of nadolol stereoisomers by multicolumn and Simulated Moving Bed adsorption processes.

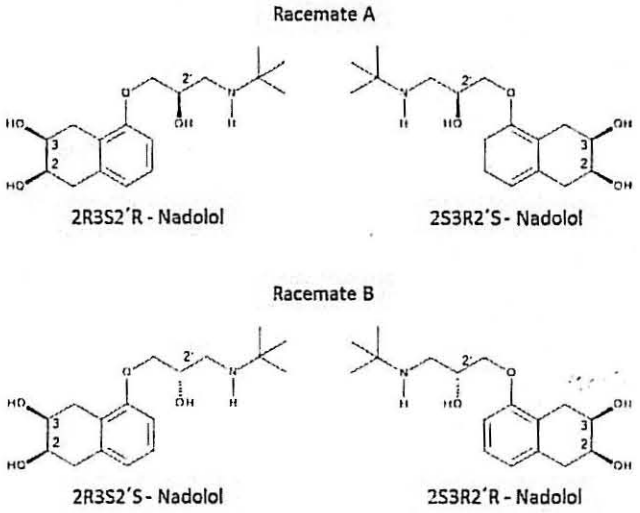

Fig. 1. Molecular structures of the four nadolol stereoisomers.

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