Separation of Nadolol Stereoisomers by Liquid Chromatography: Screening of the Mobile Phase Composition

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Abstract: The screening of the most convenient mobile phase composition is presented for the chiral separation of the four stereoisomers of the β-blocker drug nadolol. When the final goal is the preparative chiral separation, this selection is critical, since solubility, selectivity and retention are all parameters very sensitive with mobile phase composition. Experimental results will show that the "best" mobile phase composition is, generally, very different if we consider an analytical or a preparative separation point of view.

Nadolol, 5 - {3 - [(1,1 - dimethylethyl)amino] - 2 - hydroxypropoxy} - 1,2,3,4 - tetrahydro - *cis* - 2,3-naphtalenediol is a beta-adrenergic receptor antagonist (β-blocker) drug, widely used in the treatment of hypertension, ischemic heart disease (angina pectoris), congestive heart failure and certain arrhythmias (*Brunton el al., 2001*). Its chemical structure has three stereogenic centers which allows for eight possible stereoisomers (*McCarthy, 1994*). However, the two hydroxyl substituents on the cyclohexane ring are fixed in the *cis*-configuration which precludes four stereoisomers. This drug is currently marketed as an equal mixture of four stereoisomers (see Fig. 1). Separation and isolation of each of the four stereoisomers is necessary, in order to study its pharmacological and therapeutic behaviour as single enantiomer. In the case of nadolol, and for a safe and more effective use, it is better to separate the most active enantiomer (RSR)-nadolol before use (*X. Wang and C. Ching, 2003*).

Today, preparative chiral chromatography has become an attractive technology, used to obtain single enantiomeric drugs, in the biotechnology, fine chemical products and pharmaceutical industries. The chiral separation process is a complex task, governed by several different interactions between the chiral solutes, the solvent and the chiral stationary phase. In a preparative point of view, and when considering the choice of the mobile phase (solvent) composition, a high selectivity of the enantiomers should not be the only goal to be aimed, as it is frequently followed at analytical scale. In this choice, a high solubility and low retention time should also be taken into account, in order to improve the preparative process performance (*Ribeiro et al., 2008 and 2009*).

Experimental results obtained for the separation of nadolol stereoisomers include a detailed screening of different mobile phase compositions using a Chiralpak® AD stationary phase. The choice of the "best" composition is performed in terms of organic modifier (diethylamine, DEA), alcoholic content (different alcohols) in a traditional hydrocarbon solvent (different alkanes). The final conclusion for the mobile phase composition selection will be presented with the main goal of the preparative separation of nadolol stereoisomers.

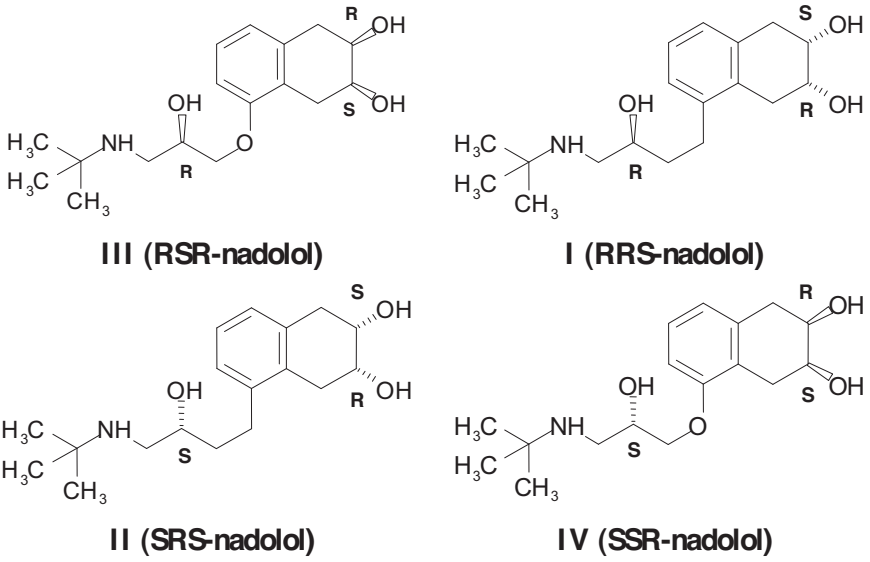

Figure 1. Chemical structures of the four stereoisomers of nadolol.

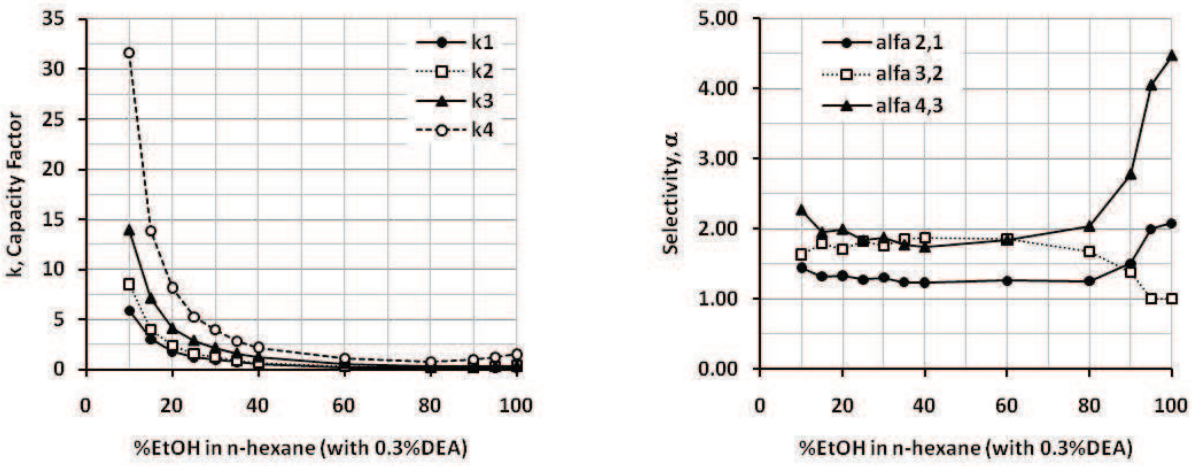

Figure 2. Effect of the ethanol content in an n-hexane mobile phase composition (with 0.3%DEA) on the capacity factor (left) and selectivity (right).

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