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Optimization of the Adsorption Process for the Analytical and Preparative Separation of Nadolol Stereoisomers

O-FP7

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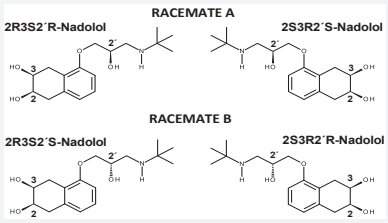

Molecular structures of the four nadolol stereoisomers

The screening of different solvents and solvents mixtures for the analytical and preparative separation of nadolol stereoisomers using two chiral stationary phases is presented.
The experimental results are analysed through different strategies of liquid chromatographic separation depending on the target compound to be separated from a quaternary chiral racemic mixture.

The wide range of present results can be very useful both for the analytical or preparative separation of nadolol in order to better characterize the pharmacological and therapeutical behaviour of all single stereoisomers of this beta-blocker pharmaceutical drug.

Introduction

The chiral separation process is a complex task, governed by several different interactions between the chiral solutes, the solvent and the chiral stationary phase (CSP). From 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 the case at analytical scale. Besides the choice of a CSP with high loading capacity, a high solubility of the solutes in the solvent and low retention times should also be taken into account, in order to improve the preparative process performance, as it was extensively explained for the separation of chiral non-steroidal anti-inflammatory drugs [1-4].

Nadolol is a non-selective beta-adrenergic receptor antagonist (beta-blocker) pharmaceutical drug, widely used in the treatment of cardiovascular system diseases. Its chemical structure has three stereogenic centers which allow for eight possible stereoisomers. However, the two hydroxyl substituents on the cyclohexane ring are fixed in the *cis*-configuration which precludes four stereoisomers [5].

The separation of nadolol stereoisomers on Chiralpak® AD at both analytical and preparative scales was recently reported by Ribeiro et al. [6]. The 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.

This work presents the main results obtained from the complete solvent screening using both the coated Chiralpak® AD and the immobilized Chiralpak® IA stationary phases. The selection of the proper CSP/solvent combination for analytical and preparative operations is fully studied taking into account the screening strategy proposed by Zhang and Franco [7]. The selection is carried out by studying the effect of different CSP/solvent combinations on the solubility, retention and resolution of the nadolol stereoisomers.

The obtained results show different possibilities to perform the separation of nadolol stereoisomers, depending on the target component or target components to be obtained. The choice of mobile phase composition is also taken based on future preparative multicomponent separations using a technology such as the Simulated Moving Bed (SMB) adsorption process.

Methodology

All analysis was performed on a Jasco HPLC system with an UV-1575 multiwavelength detector. Four chromatographic columns were used with two different sizes: analytical (sized 250mmLx4.6mmID) and preparative (sized 100mmLx20.0mmID) column, both packed with Chiralpak® AD and Chiralpak® IA CSPs. The analytical columns were pre-packed with a particle size diameter of 5 μm and the preparative columns were packed with a particle size diameter of 20 μm, using an Alltech analytical slurry packer.

The solubility measurements were performed at 23ºC by using a gravimetric method.

Several elution chromatographic pulses of a 2 g/L nadolol solution were carried out using the four analytical and preparative columns. Both Chiralpak® AD and Chiralpak® IA CSP were tested using several different alcohol/hydrocarbon mixtures and organic solvents: (1) EtOH-hexane, studying the amount of DEA; (2) EtOH-based mixtures, combining with hexane (E/C6), heptane (E/C7), methanol (E/M), dichloromethane (E/DCM), tetrahydrofuran (E/THF) or ethyl acetate (E/EtOAc); (3) ACN-based mixtures, combining with methanol (A/M), ethanol (A/E) or 2-propanol (A/P); and (4) heptane-based mixtures, combining with 2-propanol (C7/P), dichloromethane (C7/DCM), tetrahydrofuran (C7/THF) or ethyl acetate (C7/EtOAc). A qualitative and quantitative analysis was work out to better understand the effect of mobile phase composition in the performance of the chromatographic separation. For each analysis, the chromatographic resolution, retention factor, and selectivity, was evaluated.

Solubility and use of solvent additive

The solubility measurements were carried out with the mixture of the four stereoisomers of nadolol using several pure solvents. The obtained results indicate that nadolol stereoisomers solubility increases when the solvent is changed from hydrocarbons to alcohols. The results also show that nadolol is insoluble in hydrocarbons and dichloromethane and the solubility increase if the solvent is changed from butanol to 2-propanol and from this to ethanol and also from ethanol to methanol. The solubility is significantly higher using pure methanol.

The incorporation of the diethylamine (DEA) additive was studied for both CSPs. Several pulse experiments were carried out using the analytical columns, in order to optimize the amount of DEA that is necessary to the separation. The criterion was to use the minimum amount, that no significant differences in the separation were observed. This is achieved maintaining resolution between the three pairs of stereoisomers on a value of at least 1.5 and minimizing retention of the more retained stereoisomer. Results show that for Chiralpak® AD an amount of 0.3%DEA is necessary and that for Chiralpak® IA an amount of 0.1%DEA is enough to improve the separation.

Analytical separations

The 40%ethanol/60%heptane with 0.3%DEA is a better solvent composition for the analytical separation using Chiralpak® AD and four possibilities were identified using Chiralpak® IA. The 10%ethanol/90%acetonitrile presents the lowest retention value for the more retained compound and complete resolution of all stereoisomers (See Fig.1).

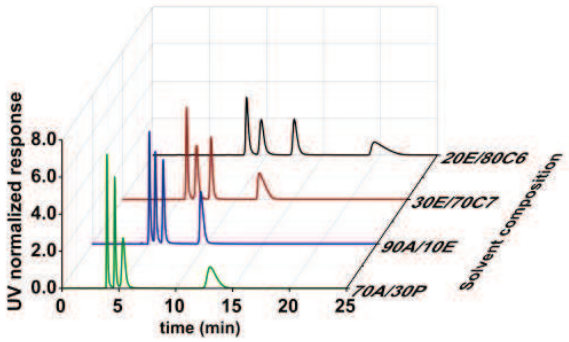

Figure 1. UV normalized response to pulse experiments of nadolol using four different mobile phase compositions. (Chiralpak® IA; C_T= 2.0 g/L; Q=1.0 mL/min; loop=20 μL).

Preparative (1+2+3)/4 separations

The set of experimental results obtained in this study can be seen as a solvent screening for a preparative separation of nadolol stereoisomers. In a first approach, we can select different possibilities for the preparative separation. Considering a preparative separation process, such as the use of simulated moving bed technology (SMB), the most retained stereoisomer will elute in the extract and the other three compounds (1, 2 and 3) will coelute in the raffinate outlet stream.

The 80%ethanol/20%heptane with 0.3%DEA is a better solvent composition for the preparative separation of the most retained stereoisomer using Chiralpak® AD.

When using the Chiralpak® IA, nine different possibilities were identified. These results show that lower retention of the more retained compound is obtained with a composition of 20%acetonitrile/80%methanol. In industry, a separation that uses a pure solvent composition is normally more acceptable than solvent mixtures, due to the practical and economical profit in recycling and recovers the solvent. Using this

perspective, pure methanol and pure ethanol compositions are both good choices for this type of preparative separation. Another important issue, that was also referred before is that solubility of nadolol is considerably higher using pure ethanol or even higher using pure methanol, a fact that could be decisive for the preparative separation performance.

Preparative (1+2+3)/4 separations

Another point of view can be considered the separation using the SMB technology and exploiting more advances modes of operation, such as the use of JO process. This mode, used as an example, allows a continuous separation of the two more retained compounds and the other two less retained co-elute together. The selection of solvent mixtures, based in this issue, can be done selecting separations with complete resolution of the third and fourth compounds and lower retention of the more retained compound. This study was conducted only with the most versatile Chiralpak® IA CSP. All the six selected solvent mixtures allows resolution of pairs 4,3 and 3,2 higher than 1.5. The separation that represents lower retention time of the more retained stereoisomer is the carried out using a 70%ethanol/30%hexane composition.

Conclusions

The use of mobile phases containing an alcohol is of utmost importance to obtain high solubility of the nadolol stereoisomers. The presence of the basic modifier (DEA) is of utmost importance to obtain resolution.

For the Chiralpak® AD stationary phase, the baseline separation of all the four nadolol stereoisomers is obtained using ethanol/hexane and ethanol/heptane compositions. The 40%ethanol/60%heptane with 0.3%DEA is a better solvent composition for analytical chromatography: it allows the baseline separation of all the four nadolol stereoisomers with a lower retention time. The 80%ethanol/20%heptane with 0.3%DEA is a suitable solvent composition for the preparative separation of the more retained stereoisomer (referred as the most therapeutically active one).

For the Chiralpak® IA CSP, besides the use of ethanol/hydrocarbon mixtures, the use of acetonitrile (with ethanol or isopropanol) also allows baseline separation of all the four nadolol stereoisomers. Good separation performance is obtained using 10%ethanol/90%acetonitrile with 0.1%DEA with low retention times. Different mobile phase compositions show potential to be used for the preparative (1+2+3)/4 and (1+2)/3/4 nadolol separations, namely: alcohol/hydrocarbon, alcohol/alcohol, alcohol/acetonitrile and alcohol/tetrahydrofuran mixtures.

Further tests will be carried out in the future to better explore all of these potential mobile phases for the SMB separation of nadolol stereoisomers using Chiralpak® IA.

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