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BOOK OF ABSTRACTS

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Influence of Mobile Phase Composition on the Preparative Separation of Profens by Chiral Liquid Chromatography

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Topic: Pharmaceutical.

The chirality of drugs is an important issue for the pharmaceutical industry, since the different enantiomers of a racemic drug may have distinct pharmacological activities, pharmacokinetic and pharmacodynamic effects. Because of its chiral selectivity, human body reacts with a racemic drug differently, and metabolise each enantiomer on separate pathways producing different pharmacological activity. Thus, one isomer may produce the desired therapeutic activities, while the other may be inactive or even, in worst cases, produce unwanted effects.

Flurbiprofen [2-(2-fluoro-4-biphenyl)-propionic acid] and ketoprofen [2-(3-benzoylphenyl)-propionic acid] belong to a family of chemicals named 2-arylpropionic acids, or profens, an important sub-class of the frequently prescribed and used drugs called nonsteroidal anti-inflammatory drugs (NSAIDs). A considerable number of these drugs possess antipyretic activity in addition to its analgesic and anti-inflammatory actions, and thus have utility in the treatment of fever. The main primary indications for NSAIDs therapy include rheumatoid arthritis, osteoarthritis, acute gouty arthritis, ankylosing spondylitis and dysmenorrhea (DeRuiter, 2002). The importance of this class of drugs is supported by the fact that, in the last twenty years, drugs like aspirin, phenazone derivatives or acetaminophen are being supplemented by profens (Brune and Hinz, 1998).

In recent literature, different analytical methods for profens can be found, including thin-layer chromatography, capillary electrophoresis, gas-liquid chromatography, supercritical fluid chromatography, and high performance liquid chromatography with UV detection. Due to its good sensitivity, reproducibility and low chromatographic interferences, high performance liquid chromatography (HPLC) using chiral stationary phases (CSPs) has been the most employed enantioseparation method of profens. The phenylcarbamate derivatives of polysaccharides, particularly cellulose and amylose, show high chiral recognition when used as CSPs for HPLC. Among the many derivatives, the amylose 3,5-dimethylphenylcarbamate (e.g. Chiralpak AD, Daicel, Japan) is the most used on the separation of profens racemates. Considering the preparative separation of this class of enantiomers, the choice of the mobile phase composition is a critical issue, since directly affects the system productivity by influencing retention time, selectivity, column efficiency and solubility of the racemate (Francotte, 2001). The objective of this work is to study how mobile phase composition, in terms of acidic and alcoholic modifiers, influences the profen enantioseparation.

The mobile phases used for profens chiral separations are usually a hydrocarbon-alcohol combination, with a high hydrocarbon content. However, profens show poor solubilities in hydrocarbon solvents. When the final objective is the high productivity preparative separations, solubility of the racemic drug is of crucial importance. Results will be presented to show that an increase of the alcoholic content in the mobile phase is possible without a decrease on selectivity.

Considering the preparative production of pure profen enantiomers using an amylose-based chiral stationary phase, results show that the optimum mobile phase needs only a small quantity of acidic

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modifier (0.01% TFA) and can be obtained under pure alcohol content. The use of pure alcohol solvents increases solubility of the racemate and decreases retention time, both advantages in a preparative scale point of view. Besides, the use of pure solvents also simplifies its reutilization in a production separation process. Considering the chiral separation of profen racemic mixtures, this work shows that the choice of the better mobile phase is not a straightforward task. Pure methanol (with a low quantity of TFA acidic modifier) should be used to separate flurbiprofen enantiomers (see Figure 1): besides higher solubility, the use of methanol presents higher selectivity and lower pressure drop. However, considering the separation of ketoprofen enantiomers, pure methanol should be replaced by pure ethanol, since the former mobile phase presents low selectivities for this system (see Figure 2).

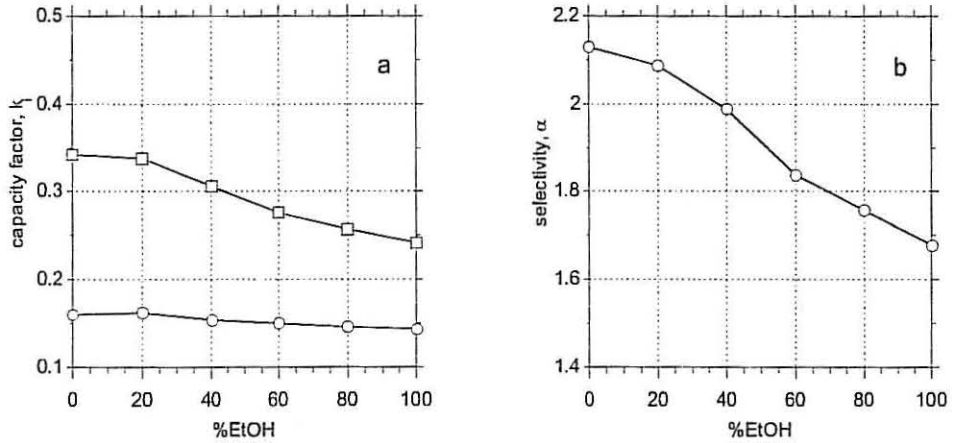

Figure 1. Effect of the content of an ethanol/methanol mobile phase on the separation parameters for flurbiprofen enantiomers: (a) capacity factors (circles for the less and squares for the more retained enantiomer); (b) selectivity (mobile phase: ethanol/methanol mixtures, with 0.01% TFA; T=25°C).

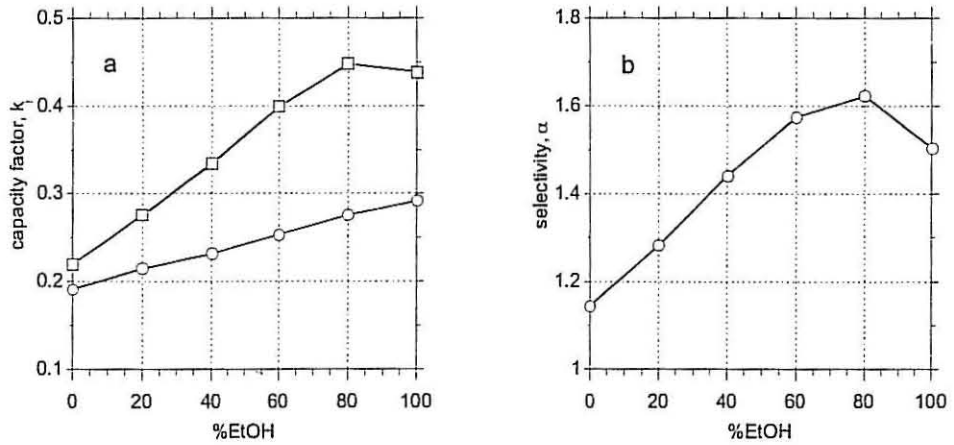

Figure 2. Effect of the content of an ethanol/methanol mobile phase on the separation parameters for ketoprofen enantiomers: (a) capacity factors (circles for the less and squares for the more retained enantiomer); (b) selectivity (mobile phase: ethanol/methanol mixtures, with 0.01% TFA; T=25°C).

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