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PRELIMINARY STUDIES FOR THE PREPARATIVE SEPARATION OF PROFENS BY CHIRAL LIQUID CHROMATOGRAPHY

A. Ribeiro[a,b], L. Pais[a,b], and A. Rodrigues[b]

[a] *School of Technology and Management, Bragança Polytechnic Institute, Campus de Sta Apolónia, Apartado 1134, 5301–857 Bragança, Portugal.*
[b] *Laboratory of Separation and Reaction Engineering, Faculdade de Engenharia da Universidade do Porto, Rua Dr. Roberto Frias, 4200-465 Porto, Portugal.*

The increasing pressure by regulatory authorities against the marketing of racemic mixtures, resulting from considerations of clinical efficacy and consumer safety, led to current efforts in the development of sensitive and efficient techniques.[1] Preparative chiral chromatography is getting increasing attention nowadays. One reason chromatography is preferred is that the process results in both high yields and purities of both enantiomers. On the other hand, this technique is applicable to a wide variety of racemic mixtures, since chromatographic stationary phases for enantiomer separation are now available. Flurbiprofen and ketoprofen belong to a family of chemicals named 2-arylpropionic acids, or profens, an important sub-class of the frequently used drugs called nonsteroidal anti-inflammatory drugs (NSAIDs). They have potent analgesic and antipyretic proprieties and are prescribed to relieve inflammation when associated to diseases such as rheumatoid arthritis, osteoarthritis, acute gouty arthritis, ankylosing spondylitis and dysmenorrheal.[2] The separation of these drugs is of special interest because his use has been associated with a number of undesirable side effects and it is believed that different enantiomers have distinct pharmacological activities and consequently different clinical effects.[3,4] In present work, liquid chromatography of profens is carried out using an amylose-based stationary phase. The optimization of chiral separations in these adsorbents is frequently a complex task since some factors are related to the proprieties of the chiral stationary phase, while others are related to the proprieties of the racemate. In this task the choice of the proper mobile phase is of crucial importance since selectivity, retention time and solubility of the racemate are very sensitive in changes on mobile phase composition.[5,6] Additionally, in a preparative perspective, pressure drop can also be a reason to change the mobile phase composition. The mobile phases used for profens chiral separations are usually a hydrocarbon-alcohol combination, with higher hydrocarbon content. However, profens show poor solubility in hydrocarbon solvents when compared to alcohols. When the final objective is high productivity preparative separations, solubility of the racemic drug is of crucial importance. This work shows that an increase of the alcoholic content in the mobile phase is possible without a decrease on selectivity. Considering the chiral separation of ketoprofen and flurbiprofen enantiomers, results show that the mobile phase needs only a small quantity of acidic modifier (0.01% TFA), and can be composed by an high alcoholic content (80-100% ethanol). Solubility studies were carried out using different solvents and results show that solubility in methanol is 60 g/100 g, higher than in ethanol (50 g/100 g). In this way, the use of methanol instead of ethanol may be considered when the objective is to separate flurbiprofen enantiomers: besides higher solubility, the use of methanol presents higher selectivity and lower pressure drop. However, the separation of ketoprofen enantiomers must be carried out using ethanol, since the use of methanol presents very low selectivities.

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