P.2 **Preparative separation of profen enantiomers by liquid chromatography**

A. Ribeiro[a, b]; N. Graça[a]; L. Pais[a, b, *]; and A. Rodrigues[b]

LSRE – Laboratory of Separation and Reaction Engineering

a Escola Superior de Tecnologia e de Gestão, Instituto Politécnico de Bragança, Campus de Stª Apolónia, Apartado 1134, 5301-857 Bragança, Portugal.

b Faculdade de Engenharia, Universidade do Porto, Rua Dr. Roberto Frias, 4200-465 Porto, Portugal.

*Corresponding author:

tlf. +351.273.303090

fax +351.273.313051

pais@ipb.pt

Profens, or 2-arylpropionic acids, are an important sub-class of the frequently prescribed non-steroidal anti-inflammatory drugs (NSAIDs). Some of the main primary indications for NSAIDs therapy include rheumatoid arthritis, osteoarthritis, acute gouty arthritis, dysmenorrhea and acute pain. Ketoprofen (R,S)-2-(3-benzoylphenylpropionic acid) and Flurbiprofen (R,S)-2-(2-fluoro-4--biphenylpropionic acid) are examples of NSAIDs, both marketed as racemic mixtures.

It was previously believed that the anti-inflammatory properties of profens reside exclusively in its S-enantiomer, while the R-enantiomer was responsibly for the undesired toxic side effects of these drugs. However, research showed that the R-enantiomers of profens have also a therapeutic action. The R-enantiomer of ketoprofen is now known to have an analgesic and antipyretic action, while the R-enantiomer of flurbiprofen is referred to promote active inhibition on the growth of a variety of human cancer and to slow the progression and pathogenesis of Alzheimer's disease.

In this scenario, the need for the separation of racemic drugs and the consequent use of pure enantiomers has increased and preparative chiral liquid chromatography has become an important separation process for the purification of pharmaceuticals and other added-value products.

The main goals of a chromatographic separation change when moving from an analytical to a preparative scale. Enantioselectivity is commonly the target parameter to be optimized at an analytical scale. However, apart from selectivity, a high loading capacity is an important requisite in preparative separations since this will affect productivity. Additionally, high throughputs in continuous separation processes, such as Simulated Moving Bed (SMB) technology, can be achieved only when high feed concentrations and short cycle times are applied. Thus, it is also necessary a correct selection of the mobile phase composition since it will affect racemate solubility, selectivity and retention times.

This work intends to investigate how mobile phase composition influences the adsorption behavior of ketoprofen and flurbiprofen enantiomers. Results will be shown considering solubility measurements and pulse and breakthrough experiments under preparative conditions to measure and test adsorption isotherms. Additionally, the competitive adsorption isotherms measurements are used to predict and compare the performance of the fixed-bed and SMB processes for the separation of both ketoprofen and flurbiprofen enantiomers.

Results show that, for ketoprofen enantioseparation, pure ethanol is a better mobile phase than the usual high alkane content mobile phases: it allows higher solubility of the racemate, lower retention times, and also higher selectivity at high enantiomer concentrations. For the flurbiprofen enantioseparation, a 10%ethanol/90%n-hexane is proposed: in spite of lower solubility (when compared with a higher polar content mobile phase), high selectivity values are achieved under preparative conditions and also within an acceptable retention time.

These results show that individual studies must be carried out for each enantioseparation system, since different profen drugs can show different behaviours.