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BRAGA, PORTUGAL

This volume contains full papers presented at the 10<sup>th</sup> International Chemical and Biological Engineering Conference - CHEMPOR 2008, held in Braga, Portugal, between September 4th and 6th, 2008.

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## **Foreword**

This digital book contains the full papers presented at the 10th International Chemical and Biological Engineering Conference - CHEMPOR 2008, held in Braga, Portugal, over 3 days, from the 4<sup>th</sup> to the 6<sup>th</sup> of September, 2008. Previous editions took place in Lisboa (1975, 1889, 1998), Braga (1978), Póvoa de Varzim (1981), Coimbra (1985, 2005), Porto (1993), and Aveiro (2001).

The conference was jointly organized by the University of Minho, "Ordem dos Engenheiros", and the IBB - Institute for Biotechnology and Bioengineering with the usual support of the "Sociedade Portuguesa de Química" and, by the first time, of the "Sociedade Portuguesa de Biotecnologia".

Thirty years elapsed since CHEMPOR was held at the University of Minho, organized by T.R. Bott, D. Allen, A. Bridgwater, J.J.B. Romero, L.J.S. Soares and J.D.R.S. Pinheiro. We are fortunate to have Profs. Bott, Soares and Pinheiro in the Honor Committee of this 10<sup>th</sup> edition, under the high Patronage of his Excellency the President of the Portuguese Republic, Prof. Anibal Cavaco Silva. The opening ceremony will confer Prof. Bott with a "Long Term Achievement" award acknowledging the important contribution Prof. Bott brought along more than 30 years to the development of the Chemical Engineering Science, to the launch of CHEMPOR series and specially to the University of Minho. Prof. Bott's inaugural lecture will address the importance of effective energy management in processing operations, particularly in the effectiveness of heat recovery and the associated reduction in greenhouse gas emission from combustion processes.

The CHEMPOR series traditionally brings together both young and established researchers and end users to discuss recent developments in different areas of Chemical Engineering. The scope of this edition is broadening out by including the Biological Engineering research. One of the major core areas of the conference program is life quality, due to the importance that Chemical and Biological Engineering plays in this area. "Integration of Life Sciences & Engineering" and "Sustainable Process-Product Development through Green Chemistry" are two of the leading themes with papers addressing such important issues. This is complemented with additional leading themes including "Advancing the Chemical and Biological Engineering Fundamentals", "Multi-Scale and/or Multi-Disciplinary Approach to Process-Product Innovation", "Systematic Methods and Tools for Managing the Complexity", and "Educating Chemical and Biological Engineers for Coming Challenges" which define the full papers arrangements along this book.

A total of 516 extended abstracts are included in the Abstract Book, consisting of 7 invited lecturers, 15 keynote, 105 short oral presentations given in 5 parallel sessions, along with 6 slots for viewing 389 poster presentations. This companion CD-ROM contains the Proceedings with 384 full papers. All extended abstracts have been reviewed and we are grateful to the members of scientific and organizing committees for their evaluations. It was an intensive task since 610 submitted abstracts from 45 countries were received.

It has been an honor for us to contribute to setting up CHEMPOR 2008 during almost two years. We wish to thank the authors who have contributed to yield a high scientific standard to the program. We are thankful to the sponsors who have contributed decisively to this event. We also extend our gratefulness to all those who, through their dedicated efforts, have assisted us in this task.

On behalf of the Scientific and Organizing Committees we wish you that together with an interesting reading, the scientific program and the social moments organized will be memorable for all.

Braga, September 2008

Eugénio C. Ferreira

Manuel Mota

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## Optimization of Mobile Phase Composition for Preparative Separation of Profens Enantiomers by Chiral Liquid Chromatography

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**Keywords:** Mobile phase composition, Preparative liquid chromatography, Chiral separation, Non-Steroidal Anti-Inflammatory Drugs, Profens.

**Topic:** Advancing the chemical engineering fundamentals.

### Abstract

In this paper it will be presented and discussed the experimental and simulation results obtained for the preparative separation of ketoprofen and flurbiprofen enantiomers by chiral liquid chromatography. Experimental results include solubility studies, elution and frontal chromatographic experiments and the measurement of competitive adsorption isotherms, using different mobile phase compositions. Modeling and simulation tools are used to predict the behavior and the performance of fixed bed and simulated moving bed processes. These prediction tools are used to select the proper mobile phase composition for the enantiomers separation in a preparative and production-scale point of view.

### 1 Introduction

Ketoprofen (R,S)-2-(3-benzoylphenylpropionic acid) and Flurbiprofen (R,S)-2-(2-fluoro-4-biphenylpropionic acid) are both examples of profens, the actual most relevant subclass of the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). These drugs are frequently prescribed worldwide in relieve of pain and in the treatment of several forms of inflammation and in the treatment of main articular diseases such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis (Burian and Geisslinger, 2005). The recent literature presents several studies concluding for different pharmacological proprieties for R and S profen enantiomers. Following these findings, chiral resolution of profen enantiomers can contribute to the development of new drugs with distinct therapeutic applications and/or safer pharmacological actions (Panico *et al.*, 2006).

The optimization of preparative chiral liquid chromatography and Simulated Moving Bed (SMB) processes is a complex task that requires a careful selection of mobile phase composition. In this selection, high resolution (or high selectivity) is not the only aspect, since other parameters, such as high solubility and low retention times, are crucial aspects that must also be considered (Ribeiro *et al.*, 2008).

In this work, experimental results obtained for the ketoprofen and flurbiprofen enantiomers will be shown, including solubility and adsorption measurements, and pulse and breakthrough experiments. Additionally, simulation results, based on the experimental adsorption isotherms measured, will be presented to compare the performance of fixed-bed and SMB processes.

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## 2 Experimental tools, modeling and simulation

The experimental tools, modeling and simulation procedures for the optimization of mobile phase composition are described in a recent published work (Ribeiro *et al.*, 2008). This includes experimental methods for solubility and adsorption isotherms measurements, and simulation tools to predict the operation of fixed-bed and simulated moving bed processes.

## 3 Results and Discussion

### 3.1 Solubility of profen racemic mixtures

Firstly, the solubility of ketoprofen and flurbiprofen enantiomers was measured in three pure solvents, all with a composition of 0.01%TFA: 100%n-hexane, 100%ethanol and 100%methanol. These solubility measurements were performed in duplicate and at a temperature of 23°C (room temperature). Obtained results (not shown) indicate that profens solubility increases when the solvent is changed from 100%n-hexane to 100% ethanol and from this to 100% methanol. On a second stage, the dependency of solubility with the alcoholic composition in an ethanol/n-hexane mixture was investigated. Results were consistent with the previous ones. Ketoprofen and flurbiprofen enantiomers have high solubility values in solvents with a high polar composition. On the other hand, a mobile phase with an increased polar content is referred as an advantage in preparative chromatography due, not only because it allows higher racemate solubility, but also because presents lower retention times (Lynam and Stringham, 2006).

### 3.2 Elution chromatography

Several experiments of elution chromatography (pulses) were performed on different solvent mixtures of ethanol/n-hexane and methanol/n-hexane, in order to characterize the system selectivity at preparative conditions. A preparative column (Chiralpak AD, Daicel, Japan), with a particle size of 20  $\mu\text{m}$ , was used on these experiments. Six level concentrations were prepared in the range between 0.05 and 4.0 g/L, and injected using two different loops: 100  $\mu\text{L}$  and 1 mL. Obtained results are presented in Figure 1, for ketoprofen, and in Figure 2, for flurbiprofen.

For ketoprofen enantiomers, results show that the 20%ethanol/80%n-hexane mobile phase presents considerable higher retention times than the pure mobile phases (ethanol and methanol). The hydrocarbon mobile phase also leads to important chromatographic tails, which is an indication of strong non-linear behavior and not welcome for preparative separations. Comparing the results obtained for the two pure alcohol mobile phases it can be clearly concluded that, despite higher ketoprofen solubility, pure methanol does not allows acceptable selectivity values and, consequently, ketoprofen enantioseparation.

For the flurbiprofen enantiomers, high selectivity values can be obtained for mobile phase compositions lower than 10%ethanol/90%h-hexane (results not shown). However, this mobile phase composition exhibits retention times substantially higher and very low solubility values, which means a clear disadvantage for high productivities. For an ethanol/n-hexane-based mobile phase, a 10/90 composition represents a reasonable compromise between selectivity, retention time and solubility. For methanol/n-hexane-based mobile phase, due to the immiscibility range between 6% and 60% methanol, its use is not possible. Taking into account the very low solubility values, experiments with less than 6% of methanol in n-hexane were also not carried out, since they are not attractive under preparative point of view. On the other side, and despite high solubility, the use of a mobile phase with higher methanol content (more than 60%) does not allow selectivity values as the ones obtained with ethanol/n-hexane mixtures.

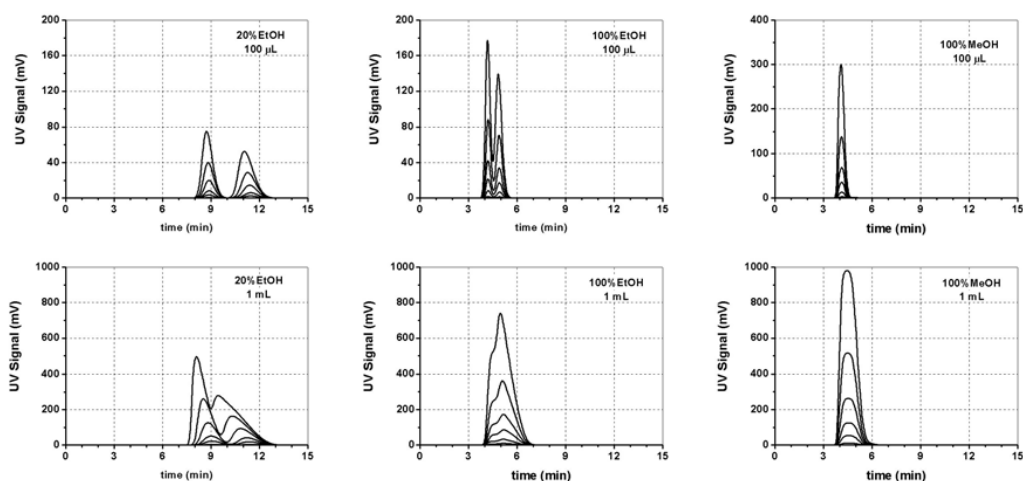


Figure 1. Experimental elution profiles of ketoprofen enantiomers in different mobile phase compositions: 20%ethanol/80%n-hexane, 100%ethanol and 100%methanol. Racemic ketoprofen concentrations in six different levels: 0.05, 0.2, 0.5, 1.0, 2.0 and 4.0 g/L; preparative column (particle diameter of 20  $\mu\text{m}$ ); UV detection at 260 nm; flow rate of 1 mL/min; temperature of 23°C; injection volumes of 100  $\mu\text{L}$  and 1 mL.

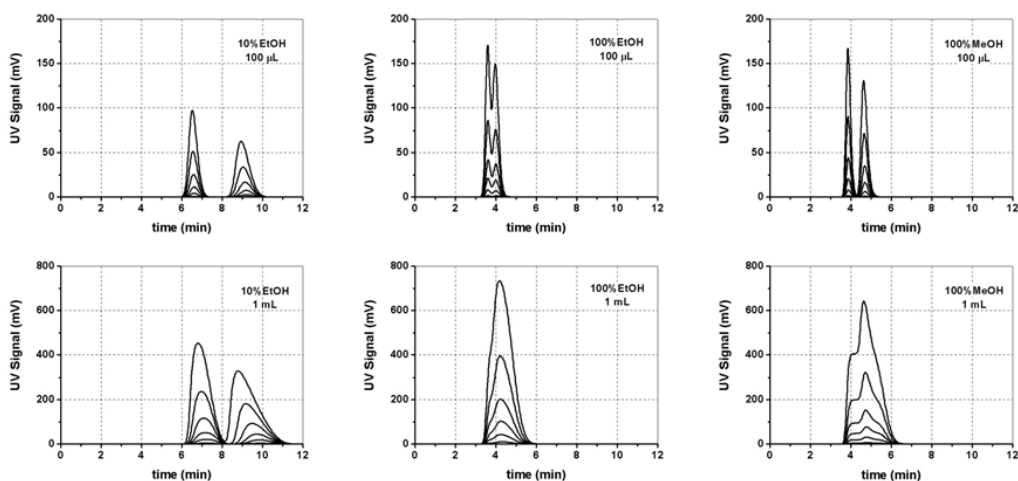


Figure 2. Experimental elution profiles of flurbiprofen enantiomers in different mobile phase compositions: 10%ethanol/90%n-hexane, 100%ethanol and 100%methanol. Racemic flurbiprofen concentrations in six different levels: 0.05, 0.2, 0.5, 1.0, 2.0 and 4.0 g/L; preparative column (particle diameter of 20  $\mu\text{m}$ ); UV detection at 260 nm; flow rate of 1 mL/min; temperature of 23°C; injection volumes of 100  $\mu\text{L}$  and 1 mL.

### 3.3 Multicomponent adsorption isotherm experiments and modeling

Figure 3 (for ketoprofen) and Figure 4 (for flurbiprofen enantiomers) present the experimental results obtained for the adsorption isotherms measurements in different mobile phase compositions, showing a good agreement with model predictions. In these figures, the prediction of the selectivity factor and its concentration dependency is also represented.

Ketoprofen results clearly show three different situations: for 100%methanol, selectivity is low and constant, which means that the separation of ketoprofen enantiomers hardly can be achieved using pure methanol as mobile phase. Despite its high selectivity for low concentrations, the common 20%ethanol/80%n-hexane mobile phase presents a strong decrease in selectivity with the increase of enantiomers concentrations. The better situation

is obtained for 100%ethanol, where selectivity maintains high values even for high enantiomer concentrations.

Results obtained for flurbiprofen enantiomers confirm a decrease in selectivity with the increase of the alcoholic content. High selectivity values can be observed for high hydrocarbon content. However, this mobile phase composition exhibits retention times substantially higher and very low solubility values. As stated before, for the separation of the flurbiprofen enantiomers, a 10%ethanol/90%n-hexane mobile phase composition is a reasonable compromise between selectivity, retention time and solubility.

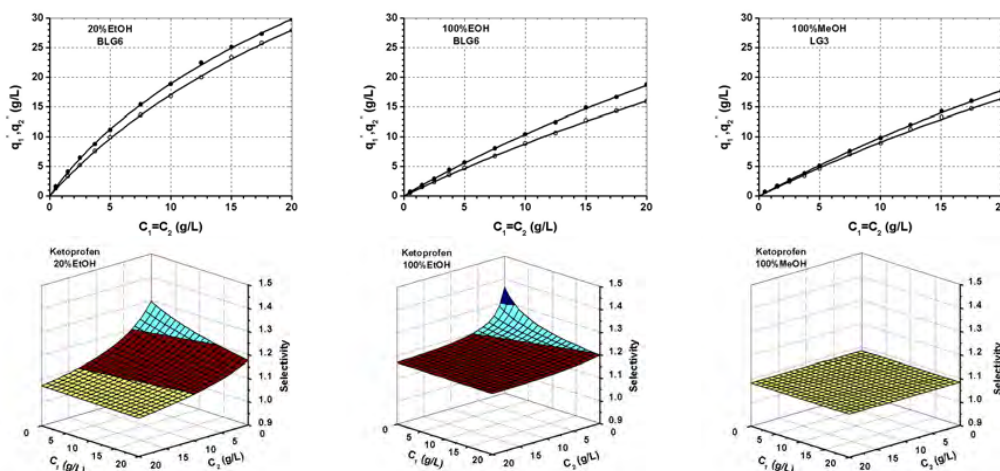


Figure 3. Comparison between model and experimental results for the equilibrium adsorption isotherms of ketoprofen enantiomers using the bi-Langmuir model (BLG6) in 20%ethanol/80%n-hexane and 100%ethanol and using the Langmuir model (LG3) in 100%methanol. Open and closed circles for the experimental concentration of the less and the more retained enantiomer, respectively; solid lines for the adsorption isotherm model. Temperature: 23°C. The second line presents the prediction of the selectivity factor as a function of both enantiomers concentration.

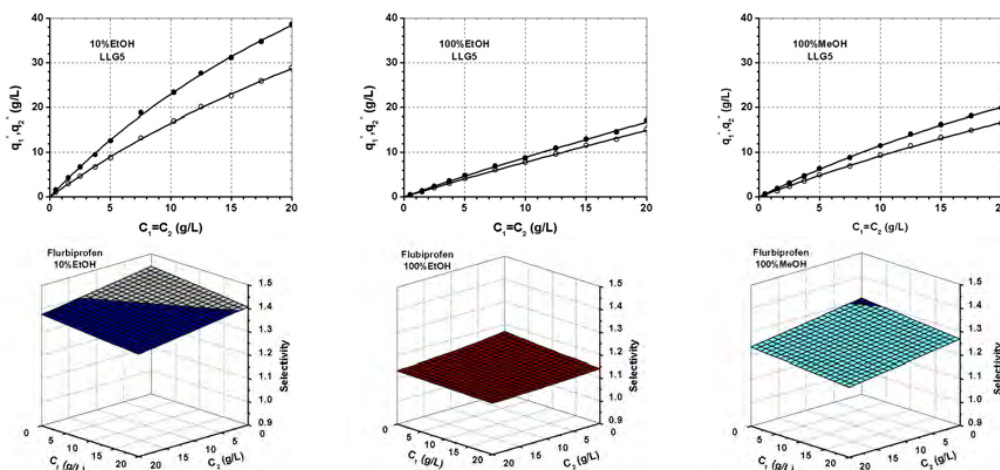


Figure 4. Comparison between model and experimental results for the equilibrium adsorption isotherms of flurbiprofen enantiomers using the modified linear+Langmuir model (LLG5) in 10%ethanol/90%n-hexane, 100%ethanol and 100%methanol. Open and closed circles for the experimental concentration of the less and the more retained enantiomer, respectively; solid lines for the adsorption isotherm model. Temperature: 23°C. The second line presents the prediction of the selectivity factor as a function of both enantiomers concentration.

### 3.4 Frontal chromatography experiments and simulation

Breakthroughs experiments were carried out with the purpose of testing the selected adsorption isotherm models. In the present work it is shown experiments using a racemic feed solution of 40 g/L and the selected mobile phase composition: 100% ethanol for the ketoprofen and 10% ethanol/90% n-hexane for flurbiprofen enantiomers. It can be clearly observed from Figure 5 that both the selected models describe very well the experimental data behaviour in the whole concentration range.

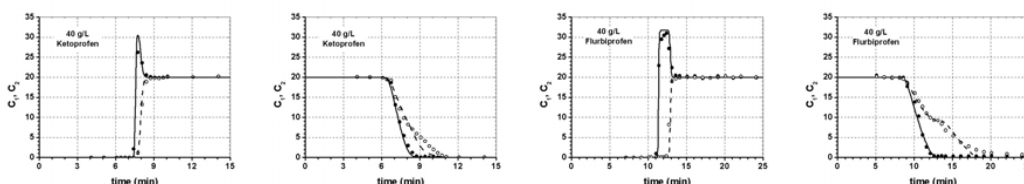


Figure 5. Saturation (adsorption) and regeneration (desorption) curves for a racemic feed concentration of 40 g/L. Comparison between experimental (points) and simulation (lines) results. Closed and open circles for the less and the more retained enantiomer, respectively. Temperature: 23°C. Flow rate: 0.5 mL/min. Ketoprofen: 100% ethanol and bi-Langmuir model (BLG6); Flurbiprofen: 10% ethanol/90% n-hexane and modified linear+Langmuir model (LLG5). Model parameters:  $\epsilon=0.4$ ,  $Pe=3500$ ,  $St=kt=1000$  (see Ribeiro *et al.*, 2008).

### 3.5 Performance of SMB operation

The performance of the ketoprofen enantiomers separation by SMB technology is compared in Figure 6 for different mobile phase compositions using the Equilibrium Theory model. The separation region (see plot  $\gamma_2$  vs  $\gamma_1$ ) for 20% ethanol/80% n-hexane has operating conditions considerable different from the ones obtained for the pure alcohol mobile phases (pure ethanol and pure methanol) due to the higher retention times. Comparing the separation regions for the three mobile phases, it can be concluded that, for the 20/80 composition, the separation region becomes quickly smaller with the increase of feed concentration. This is a sign of stronger non-linear behavior of the adsorption process and a reason for lower productivities.

The comparison of the SMB performance for the two pure alcohol mobile phases is clear: both have similar operating conditions due to similar retention times, but pure ethanol presents considerable better performances due to higher selectivity. Figure 6 also presents the productivity and the solvent consumption obtained for the different mobile phase compositions, as a function of feed concentration. These simulation results also clearly show that pure ethanol is the better choice for the separation of ketoprofen enantiomers through SMB operation: at high feed concentrations, the productivity using pure ethanol is three times the ones obtained with the other two solvents, and solvent consumption is only 75% and 25% of the one needed with pure methanol and 20% ethanol/80% n-hexane, respectively.

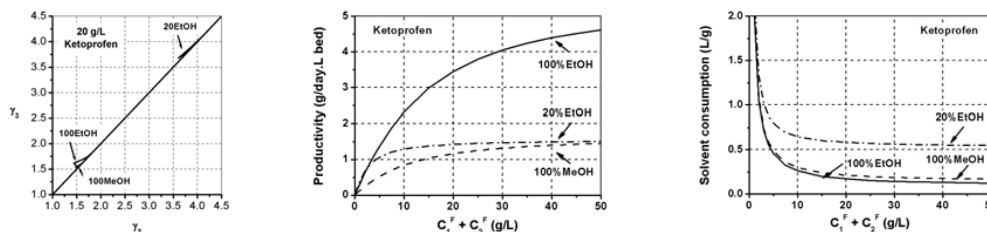


Figure 6. SMB separation regions and prediction of the performance of SMB operation for ketoprofen enantiomers: productivity and solvent consumption as a function of feed concentration for the different mobile phase compositions.

For flurbiprofen enantiomers (see Figure 7) it can be observed high retention time values in mobile phases with high hydrocarbon contents (the separation regions are progressively located at higher values of  $\gamma_2$  and  $\gamma_3$  with an increase of the n-hexane content). On the other side, these results are very different from the ones obtained for the separation of the ketoprofen enantiomers. The dimension of the separation regions progressively decrease with the decrease of the n-hexane content (increase of the ethanol content). Therefore, the best performance (bigger separation region) is obtained with a 10% ethanol/90% n-hexane composition through all feed concentration range. The performance parameters predictions also support the previous conclusions. Under preparative conditions, maximum productivity is achieved with the 10/90 composition, while solvent consumption does not significantly differ for all mobile phase compositions.

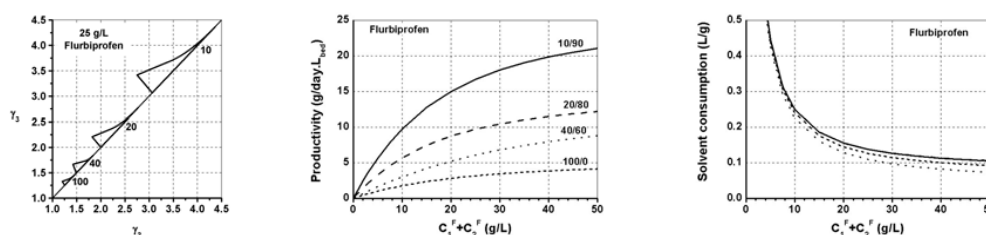


Figure 7. SMB separation regions and prediction of the performance of SMB operation for flurbiprofen enantiomers: productivity and solvent consumption as a function of feed concentration for the different mobile phase compositions.

#### 4 Conclusions

For the separation of ketoprofen enantiomers, best situation is achieved using pure ethanol as mobile phase. For flurbiprofen enantiomers, the experimental results obtained lead to different conclusions: a 10% ethanol/90% n-hexane composition is the better choice since it represents a good compromise between selectivity, retention time and solubility. The present work shows that the choice of the proper mobile phase composition is a topic of utmost importance for the optimization of preparative liquid chromatographic separations. This choice will affect the throughput of the separation process since solubility, retention time, and selectivity are all parameters very sensitive to changes in mobile phase composition.

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#### References

- Burian, M., Geisslinger, G. (2005). *COX-dependent mechanisms involved in the antinociceptive action of NSAIDs at central and peripheral sites*. Pharmacol. Ther. 107, 139-154.
- Lynam, K., Stringham, R. (2006) *Chiral Separations on Polysaccharide Stationary Phases Using Polar Organic Mobile Phases*. Chirality 18, 1-9.
- Panico, A., Cardile, V., Gentile, B., Garuti, F., Avondo, S., Rosivalle, S. (2006). *"In vitro" differences among (R) and (S) enantiomers of Profens in their activities related to articular pathophysiology*. Inflammation 29, 119-128.
- Ribeiro, A., Graça, N., Pais, L., Rodrigues, A. (2008). *Preparative separation of ketoprofen enantiomers: Choice of mobile phase composition and measurement of competitive adsorption isotherms*. Sep. Pur. Technol. 61, 375-383.