Ribeiro, A., **Pais**, L., and Rodrigues, A.

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

in *ChemPor'2005 9th International Chemical Engineering Conference*, Coimbra, Portugal, 21st -23rd September, 2005.

(poster)

CHEMPOR 2005

Coimbra – 21st – 23rd September 2005

PROGRAMME

Wednesday 21 st September

18:00-19:30 Welcoming participants

Thursday 22nd September

Anfiteatro 1

08:30-09:00 Welcoming participants

09:00-09:30 Opening Session

Session 1 Chairpersons: *F. Ramôa Ribeiro* and *Lélio Quaresma Lobo*

09:30-10:15 Invited Lecture: Dr.Trevor Evans (Chief Executive& Secretary IchemE);
"The role of National Societies and the European Federation of Chemical Engineering in promoting a better appreciation of chemical engineering as an essential contributor to the quality of life and to achieving a suitable future."

10:15-11:00 Invited Lecture: Prof. Jens Nielsen (Technical University of Denmark)
"The role of chemical engineering in modern biotechnology."

11:00-11:15 Coffee Break

Anfiteatro 1

Session 2 Chairpersons: *Moura Bordado* and *Salvador Pinheiro*

11:20-12:05 Invited Lecture Engº C. Pedro Nunes (CUF)
Uma Perspectiva Estratégica da Indústria da Refinação de Petróleos e Petroquímica em Portugal.
Chairpersons: *Moura Bordado* and *Salvador Pinheiro*

12:05-12:25 IP006- **Methylacetylene and Propadiene Reactors Optimization in the Sines Repsol Steam Cracker Plant**
André A.Vilelas, José P. Braga
Interface Team, Olefins Plant, Repsol Steam Cracker,Sines, Portugal.

12:25-12:45 IP034- **Study and optimization of a hydrogen distribution network: refinery case study**
André Fonseca, Vítor Sá, Hugo Bento, Manuel L.C. Tavares, Luísa A.C.N. Gomes
Chemical Engineering Department, Instituto Superior de Engenharia, IPP, Porto;
Technology Area, Galp Energia, 4451-852 Leça da Palmeira, Portugal.

12:45-13:05 IP010- **Separation of branched hexane isomers on zeolite BETA**
Patrick S. Bárcia, José A. C. Silva, Alírio E. Rodrigues
Escola Superior de Tecnologia e Gestão, Instituto Politécnico de Bragança;
Laboratory of Separation and Reaction Engineering, Departamento de Engenharia Química, FEUPorto.

13:05-13:25 IP068- **Recuperação do ciclohexanol e da ciclohexanona do processo de produção de anilina**
Fernando P. Mendes, Marco A. F. Prior, Rui M. F. Andrade, Susana C. G. Caldas, Mário Jorge O. Pinho, Laura M. T. Santos, Luís M. Castro, Nazaré C. Pinheiro, Manuel A. Ramos, Belmiro P. M. Duarte
Quimigal S.A., Química de Portugal, Portugal;
Departamento de Engenharia Química, Instituto Superior de Engenharia de Coimbra.

13:25-13:45 MSC031-**Multivariate analysis of the benzene nitration process for pollution prevention**
Paulo A. Quadros, Marco S. Reis, Cristina M. S. G. Baptista
Gepsi-PSE Group, Chemical Engineering Department, University of Coimbra.

Anfiteatro 2

Session 3 Chairpersons: *Alírio Rodrigues* and *Rosa Quinta Ferreira*

12:05-12:25 ESF005-**Efeito protector da matriz em catalisadores de "cracking" catalítico em relação ao envenenamento por bases azotadas**
G. Caeiro, Patrick Magnoux, J.M. Lopes e F. Ramôa Ribeiro
CEBQ, Instituto Superior Técnico, Lisboa ; Lab. de Catalyse en Chimie Organique, Poitiers, France

12:25-12:45 ESF021- **Degradação fotocatalítica de corantes têxteis**
Edilberto T. Soares, Marla A. Lansarin, Celso C. Moro, Cristina L. Souza e Natália Klafke

16:25-16:45 ESF051- **Effect of hydrodynamic conditions in osmotic evaporation using membrane contactors**
V. D. Alves, I. M. Coelhoso
REQUIMTE / CQFB, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa.

Anfiteatro 3

Session 16 Chairpersons: *Ana Paula Póvoa and Adélio Mendes*

16:05-16:25 QL082-**Protein recovery from tannery wastewater containing chromium by nitrogen removal**
Francisco N.S. Basilio, Helder F.C. Marques, Marta I.G. Sousa, Raquel A.P. Silva, Nídia S. Caetano
Chemical Engineering Department, Instituto Superior de Engenharia do Porto;
LEPAE, Chemical Engineering Department, Instituto Superior de Engenharia do Porto.

16:25-16:45 QL111-**Preparation of Therapeutic Contact Lenses Using Supercritical and Compressed Fluids**
Hermínio C. de Sousa, Ana Rita C. Duarte, Joana P. Guerra, Viviana P. Costa, Eugénio O.B. Leite, Catarina M.M. Duarte, Maria H. Gil
Departamento de Engenharia Química, Faculdade de Ciências e Tecnologia, Universidade de Coimbra;
Instituto de Biologia Experimental e Tecnológica, Oeiras;
Faculdade de Ciências da Saúde, Universidade da Beira Interior, Covilhã.

Anfiteatro 4

Session 17 Chairpersons: *António Portugal*

16:05-16:25 QL115-**Life Cycle Assessment of bioethanol from sugar beet and wheat – comparison with gasoline**
João Malça, Fausto Freire
Mechanical Engineering Department, ISEC, Coimbra Polytechnic Institute;
Mechanical Engineering Department, Faculty of Sciences and Technology, University of Coimbra.

16:25-16:45 QL090-**The emergence of a new field of application of chemical and systems engineering principles: pharmaceutical engineering**
José Cardoso de Menezes
Centre for Chemical & Biological Engineering, IST, Technical University of Lisbon.

16:45-17:00 Coffee Break

Anfiteatro 1

Session 18 Chairpersons: *Sebastião Feyo de Azevedo* and *Pedro Saraiva*

17:00-17:40 Chemical Engineering Education – Prof. Robert Armstrong, MIT, USA
"Frontiers in Chemical Engineering Education."

17:40-18:40 Forum Chemical Engineering Education

18:40-19:00 Closing Session

POSTER SESSIONS

Thursday 22nd September

17:20-19:00 Chemical Engineering Department

ESF-Engineering Sciences and Fundamentals

ESF001 - **Mass transfer to clean bubbles at low turbulent energy dissipation**
Sebastião S. Alves, Jorge M. T. Vasconcelos, Sandra P. Orvalho,
Centro de Eng. Biológica e Química, Dept. of Chemical Engineering, Instituto Superior Técnico, Lisboa, Portugal.

ESF003 - **Plug Formation and Flow Regimes in Dense-Phase Pneumatic Conveying**
Fernando A. V. Silvano, Severino S. Pandiella
Departamento de Engenharia Mecânica, Escola Superior de Tecnologia e Gestão, Instituto Politécnico de Leiria, Leiria, Portugal.
School of Chemical Engineering and Analytical Science, The University of Manchester, Manchester, U. K.

ESF004 -**Dynamic model of a supercritical carbon dioxide heat exchanger**
João B. Fernandes, Pedro C. Simões, José Paulo Mota
REQUIMTE, Chemistry Department, University Nova of Lisbon, Quinta da Torre, Caparica, Portugal.

ESF006 -**Safety study for scaleup of dehydroabietic acid**
Carlos Lopes, Carla Raminhos, João A.A. Lourenço
Instituto Nacional de Engenharia e Tecnologia Industrial, Lisboa, Portugal.

José P.B. Mota
Requimte/CQFB, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Caparica, Portugal.

ESF068 -**Phase Equilibria Of Sulphur**
A. G. M. Ferreira1, L. Q. Lobo
Chemical Engineering Department, University of Coimbra, Coimbra, Portugal.

ESF069 -**Solubility of a Spironaphthoxazine Photochromic Dye in Supercritical Carbon Dioxide: Experimental Determination and Correlation**
Patrícia M. Coimbra, B. Mark Heron, Maria H. Gil, Catarina M.M. Duarte, Hermínio C. de Sousa
Departamento de Engenharia Química, Faculdade de Ciências e Tecnologia, Universidade de Coimbra, Coimbra, Portugal;
Instituto de Biologia Experimental e Tecnológica, Oeiras, Portugal;
Department of Colour and Polymer Chemistry, University of Leeds, Leeds, UK.

ESF070 -**Applicability of Taylor-Aris Analysis to Non-Newtonian Fluids**
Cláudio A. Filho, Carlos M. Silva, Eugénia A. Macedo, Marintho B. Quadri
Departamento de Engenharia Química e Engenharia de Alimentos - Universidade Federal de Santa Catarina – Brasil;
CICECO, Departamento de Química, Universidade de Aveiro, Campus de Santiago, Aveiro, Portugal;
LSRE - Departamento de Engenharia Química Faculdade de Engenharia da Universidade do Porto, Porto, Portugal.

ESF071 -**Kinetic Modelling of the Catalytic Cracking N-Heptane over a ZSM-5 zeolite**
R. Ramos Pinto, P. Borges, M.A.N.D.A. Lemos, F. Lemos, J.C. Védrine, E.G. Derouane, F. Ramôa Ribeiro
Centro de Engenharia Biológica e Química, Departamento de Engenharia Química, Instituto Superior Técnico, Lisboa, Portugal.
ISCSP, Polo Universitário do Alto da Ajuda, Lisboa, Portugal;
Laboratoire de Physico-Chimie des Surfaces, ENSCP, Paris, France.
Faculdade de Ciências e Tecnologia, Centro de Investigação em Quimíca e Catálise, Universidade do Algarve, Faro, Portugal.

ESF072 -**Baker's yeast filtration through mixed beds of filtration aids and large glass beads**
Manuel Mota, José A. Teixeira, Alexander Yelshin
Centro de Eng. Biológica, University of Minho, Braga, Portugal.

ESF073 -**Equilibrium Moisture Content and Heat of Desorption of Garlic**
Inês F.A. Mariz, Luís S. Pais, Filomena F. Barreiro, José A.C. Silva
LSRE Laboratory of Separation and Reaction Engineering, Instituto Politécnico de Bragança, Bragança, Portugal.

ESF074 -**Modificação pós-síntese de zeólito BEA por desaluminação ácida: caracterização catalítica das amostras**
João P. Marques, Isabelle Gener, João C. Bordado, José M. Lopes, Fernando Ramôa Ribeiro, Michel Guisnet
Centro de Engenharia Biológica e Química, Instituto Superior Técnico, Lisboa, Portugal;
Laboratoire de Catalyse en Chimie Organique, Poitiers, France.

IP- Industrial Processes

IP003 -**Soda Pulp From Abaca. Influence Of The Operational Variables**
José Luis Ferrer, Victoria Angulo, Antonio Pérez, Enrique Ramos, Alejando Rodríguez, Luis Jiménez
Departamento de Ingeniería Química, Universidad de Córdoba, Córdoba, Spain;
Servicio de Investigación del Instituto de la Vid y el Vino de Castilla-La Mancha, Tomelloso, Ciudad Real, Spain;
Departamento de Ciencias Ambientales, Universidad Pablo de Olavide, Carretera de Utrera, Sevilla, Spain.

IP009 -**Influence of Mobile Phase Composition on the Preparative Separation of Profens by Chiral Liquid Chromatography**
António E. Ribeiro, Luís S. Pais, Alírio E. Rodrigues
Laboratory of Separation and Reaction Engineering,
School of Technology and Management, Bragança Polytechnic Institute, Bragança, Portugal
Faculty of Engineering, University of Porto, Portugal

IP011 -**Multivariate and Multiscale Analysis of Paper Surface**
Marco S. Reis , Pedro M. Saraiva, Dina Angélico and José Ataíde
GEPSI – PSE Group, Department of Chemical Engineering, University of Coimbra, Coimbra, Portugal;
Portucel SA, Setúbal, Portugal.

IP013 -**Use of peracetic acid and hydrogen peroxide mixture to bleach soda abaca pulp**
I. Pérez, E. Ramos, M.J. de la Torre, L. Martínez, S.F. Calatrava, L. Jiménez, J.C., Gutiérrez, A. Rodríguez
Chemical Engineering Group, Environmental Science Department, University Pablo Olavide, Sevilla, Spain;
Chemical Engineering Department, University of Córdoba, Córdoba, Spain.

IP014 -**High Solids Alkyd Resins**
M. Boaventura, I. Fernandes, J. L. Nogueira, A.Mendes
CIN, Corporação Industrial do Norte, S.A., Maia, Portugal;
Resiquímica - Resinas Químicas, S.A., Mem Martins, Portugal;
LEPAE – Departamento de Engenharia Química, Faculdade de Engenharia, Universidade do Porto, Porto, Portugal.

IP015 -**Determinação da Permeabilidade de Revestimentos por Pintura ao Dióxido de Carbono e aos Iões Cloreto**
C. Carneiro, F.Oliveira, J. Nogueira, A.Mendes
CIN, Corporação Industrial do Norte, S.A., Maia, Portugal;

INFLUENCE OF MOBILE PHASE COMPOSITION ON THE PREPARATIVE SEPARATION OF PROFENS BY CHIRAL LIQUID CHROMATOGRAPHY

António E. Ribeiro [1,2], Luís S. Pais [1,2] & Alírio E. Rodrigues [2]

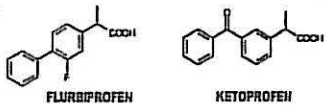
1. School of Technology and Management, Bragança Polytechnic Institute

2. Laboratory of Separation and Reaction Engineering, LSRE, School of Engineering University of Porto

INTRODUCTION:

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.

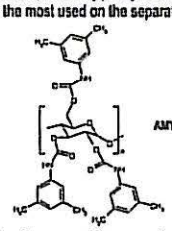
Flurbiprofen [2-(2-fluoro-4-biphenyl)-propionic acid] and ketoprofen [2-(3-benzoylphenyl)-propionic acid] belong to a family of chemicals named 2-arylpropionic acids, or profens, an important sub-class of the frequently prescribed and used drugs called nonsteroidal anti-inflammatory drugs (NSAIDs).



FLURBIPROFEN KETOPROFEN

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. 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.

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.



AMYLOSE 3,5-DIMETHYLPHENYLCARBAMATE

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. The objective of this work is to study how mobile phase composition, in terms of acidic and alcoholic modifiers, influences the profen enantioseparation.

EQUIPMENT AND MATERIALS:

Apparatus:

Jasco HPLC System containing a PU-1580 pump, an UV-1575 multiwavelength detector set at 260 nm and a manual injector Rheodyne with a 20 ml loop.

Chemicals and Materials:

Ethanol absolute, methanol, isopropyl alcohol, n-hexane and acetonitrile were all of HPLC grade, trifluoroacetic acid (TFA) spectrophotometric grade, 1,3,5-tri-*tert*-butylbenzene (as non-retained component), racemic flurbiprofen and racemic ketoprofen of analytical grade were all purchased from Sigma (Madrid, Spain).

The column used was a 10 µm Chiralpack AD (250x4.6 mm) from Daicel Chemical Industries (Japan). All separations were carried out at 25ºC using a water bath.

FORMULAE:

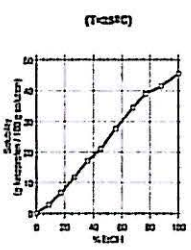
Selectivity	Capacity Factor	Height Equivalent to a Theoretical Plate
$\alpha = \frac{tr_2 - tr_0}{tr_1 - tr_0}$	$k_i = \frac{tr_i - tr_0}{tr_0}$	$HETP_i = \frac{\sigma_i^2}{t_i^2} L$

ACKNOWLEDGEMENTS:

Financial support from the portuguese R&D foundation, Fundação para a Ciência e a Tecnologia (project POCTI/38811/EQU/2001).

RESULTS AND DISCUSSION:

SOLUBILITY MEASUREMENTS:



Racemic mixture	Solvent	T (ºC)	Solubility (g/100g of solution)
Ketoprofen	Hexane	25	Insoluble
	Acetonitrile		18.1
	Isopropanol		37.7
	Ethanol	15	39.2
		20	44.8
		25	46.3
	Methanol	15	48.3
		20	56.0
		25	58.4
Flurbiprofen	80% Hexane 20% Ethanol	25	12.6
	Ethanol		34.0
	Methanol		37.2

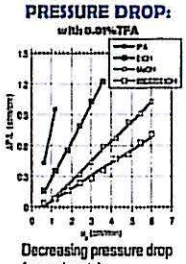
-The alcoholic (ethanol) content of the mobile phase drastically influences enantiomers solubility;

-Ketoprofen enantiomers are not soluble in a pure hexane solvent and its solubility in alcohol increases with the increase of temperature;

-At 25 ºC, ketoprofen enantiomers show increasing solubilities for pure acetonitrile, isopropyl alcohol, ethanol and methanol;

-Although showing lower solubilities than ketoprofen, the flurbiprofen enantiomers present the same increase in solubility with the increase of the alcoholic content.

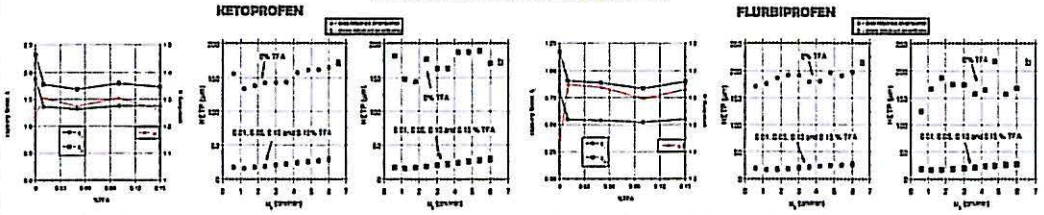
PRESSURE DROP:



Decreasing pressure drop (pure eluents): isopropanol, ethanol, methanol, and n-hexane.

EFFECT OF ACIDIC MODIFIER

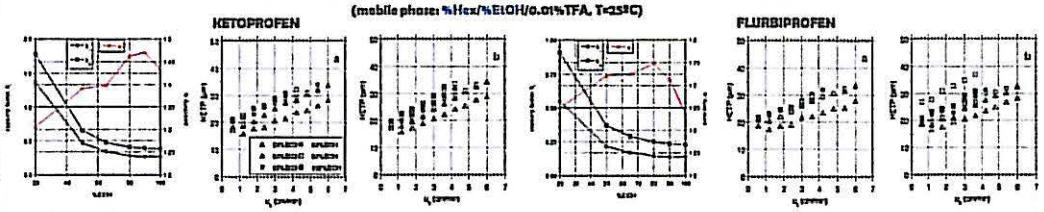
(mobile phase: 80%Hex/20%EtOH/%TFA, T=25ºC)



The results clearly show that the introduction of the acidic modifier decrease retention of both enantiomers and increase selectivity. However, it was found that a small concentration of TFA (0.01%) is enough to ensure separation and no better performances are obtained with higher TFA contents.
These results are similar for both profens (flurbiprofen and ketoprofen). Also, the same results are found when using methanol as solvent (results not showed).

EFFECT OF ALCOHOL MODIFIER: HYDROCARBON-ALCOHOL MIXTURES

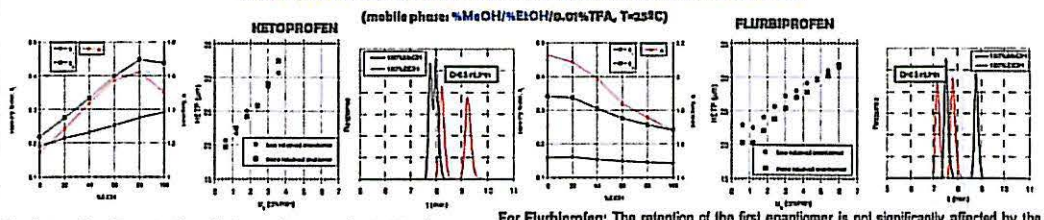
(mobile phase: %Hex/%EtOH/0.01%TFA, T=25ºC)



We conclude that retention (capacity factors) and resolution diminish with the increment of the alcoholic (ethanol) content. However, selectivity remains under relatively constant values. The same occurs in terms of column efficiency. These results reveal that the use of pure alcoholic solvents is possible for chiral separations, and beneficial at a preparative scale. Although the capacity factors substantially change with the polar modifier content, the selectivity value remains in general relatively constant. This indicates that most of the specific interactions, which determine the retention time, affect both enantiomers in a similar way, and, so, can be classified as non-chiral in nature.

EFFECT OF ALCOHOL MODIFIER: ALCOHOL-ALCOHOL MIXTURES

(mobile phase: %MeOH/%EtOH/0.01%TFA, T=25ºC)



For ketoprofen: The retention of both enantiomers and selectivity decrease with the increase of the MeOH content. Better mobile phase for ketoprofen separation: 80%EtOH/20%MeOH/0.01%TFA or even 100%EtOH/0.01%TFA.

For Flurbiprofen: The retention of the first enantiomer is not significantly affected by the composition of the MeOH/EtOH mobile phase, while the retention of the second enantiomer increases with the increase of the MeOH content. Selectivity also increases with MeOH content. Better mobile phase for flurbiprofen separation: 100%MeOH/0.01%TFA.

CONCLUSIONS:

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 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: 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.