COMPLETE DESIGN AND OPTIMIZATION OF MULTICOMPONENT SEPARATION PROCESSES

THE CASE STUDY OF A QUATERNARY SEPARATION OF NADOLOL STEREOISOMERS

LSRE LABORATORY OF SEPARATION AND REACTION ENGINEERING

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NADOLOL STEREOISOMERS

Chiral liquid chromatography is based on different mutual interactions between the molecules that elute with the liquid (solvent and solutes) and the molecules that are present in the stationary phase. Therefore, optimization of a chiral separation is based on the selection of a proper combination between a CSP and a mobile phase (solvent) composition by promoting, in a favorable way, all possible mutual interactions. The optimization will be a much more challenging task if we are leading not with a traditional binary racemic mixture separation problem but if we are interested in the separation of a quaternary chiral mixture. The complexity degree will be significantly increased if we consider a preparative separation, using a technique such as the simulated moving bed technology, were high feed concentrations are normally used in order to improve the process performance. In these situations, the wanted high concentrations of the different chiral solutes inside the chromatographic columns will enhance significantly the mutual competition between solutes for adsorption with the stationary phase.

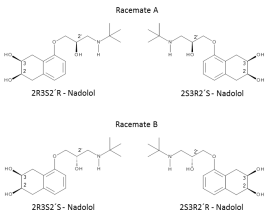
From a preparative point of view, and when considering the choice of the mobile phase ("solvent") composition, a high selectivity of the enantiomers should not be the only goal to be aimed, as it is frequently the case at analytical scale. Besides the choice of a CSP with high loading capacity, a high solubility of the solutes in the solvent and low retention times should also be taken into account, in order to improve the preparative process performance, as it was extensively explained for the separation of chiral non-steroidal anti-inflammatory drugs.

Nadolol (1-(tert-butyamino)-3-[(5,6,7,8-tetrahydro-cis-6,7-dihydroxy-1-naphthyl)oxy]-2-propanol) is a non-selective beta-adrenergic antagonist pharmaceutical drug. This class of pharmaceutical drugs is prescribed, mainly, to treat arrhythmias, angina pectoris, hypertension, migraine disorders and for tremor. Today, and in spite of the more and more restricted international legislation towards the commercialization of pharmaceutical drugs based on active principles that are made of single enantiomers, nadolol is still only commercially available as an equal mixture of four stereoisomers

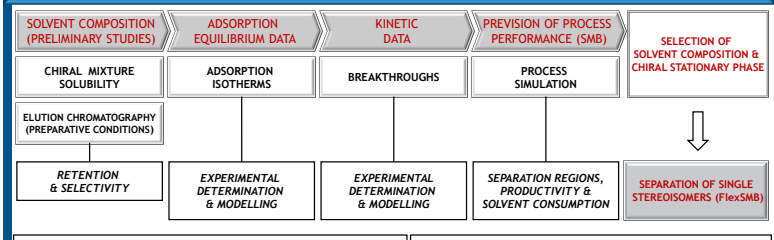
The separation of nadolol stereoisomers on CHIRALPAK® AD at both analytical and preparative scales was recently reported by Ribeiro et al. However, nowadays no further work was developed to better understand and exploit the capabilities of Chiralpak® IA both for the analytical and preparative chiral separations of nadolol stereoisomers. This work will present a complete methodology concerning experimental, modelling and simulation results. Both the CHIRALPAK® AD and CHIRALPAK® IA CSP will be evaluated. The selection of the proper CSP/solvent combination for preparative operation will be fully study taking into account the screening strategy proposed by Zhang et al. Additional results include the measurement of nadolol stereoisomers solubilities, equilibrium adsorption data and fixed bed (breakthroughs) experiments. The complete screening of CSP/solvent combination will lead to the choice of the better solutions for the separation of nadolol stereoisomers, considering the target component or components to be obtained. Simulation and experimental results will be presented for the multicomponent separation of nadolol stereoisomers by Simulated Moving Bed adsorption process.

References:

[1] A.E. Ribeiro, N.S. Graça, L.S. Pais, A.E. Rodrigues, Sep. Pur. Technol., 61, 375 (2008).
[2] A.E. Ribeiro, N.S. Graça, L.S. Pais, A.E. Rodrigues, Sep. Pur. Technol., 68, 9 (2009).
[3] A.E. Ribeiro, P. Sá Gomes, L.S. Pais, A.E. Rodrigues, Sep. Sci. Technol., 46 1726 (2011).
[4] A.E. Ribeiro, P. Sá Gomes, L.S. Pais, A.E. Rodrigues, Chirality, 23, 602 (2011).
[5] A.E. Ribeiro, A. E. Rodrigues, L.S. Pais, Chirality, 25, 197 (2013).
[6] T. Zhang, D. Nguyen, P. Franco, J. Chromatogr. A, 214, 1191 (2008).

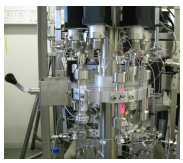


METHODOLOGY & EQUIPMENT



HPLC AND SMB APPARATUS

- Jasco HPLC System containing a PU-1580 pump, an UV-1575 multiwavelength detector set at 270 nm and a manual injector Rheodyne with 20 μL, 100 μL and 1000 μL loops.
- Three types of columns were used: a 10 μm Chiralpak AD, a 5 μm Chiralpak IA (both 250x4.6 mm) and a 20 μm Chiralpak AD (100x20 mm), named as "SMB column" from Daicel Chiral Technologies Europe (France). All separations were carried out at 23ºC. Flow rates: 1 mL/min for the two analytical columns and 5 mL/min for the SMB column.
- SMB unit (the FlexSMB) operating with 6 SMB columns and using a [1-2-2-1] configuration.



SCREENING OF MOBILE PHASE COMPOSITION CHIRALPAK® AD and CHIRALPAK® IA

Chiralpak AD (traditional MP):

- Alcohol/Hydrocarbon mixtures, with Alcohol being Methanol, Ethanol, Propanol, iso-Propanol and Butanol, and Hydrocarbon being Hexane and Heptane

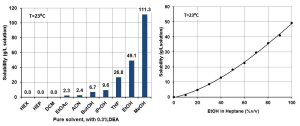
Chiralpak IA (traditional MP and also):

Same used with Chiralpak AD and also:

- Alcohol/Acetonitrile mixtures, with Alcohol being Methanol, Ethanol, and iso-Propanol
- Methanol/Ethanol mixtures
- Dichloromethane/Heptane mixtures
- Ethanol/Dichloromethane mixtures
- Tetrahydrofuran/Heptane mixtures
- Ethanol/Tetrahydrofuran mixtures
- Ethyl Acetate/Heptane mixtures
- Ethanol/Ethyl Acetate mixtures

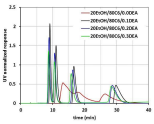
EXPERIMENTAL RESULTS

SOLUBILITY EXPERIMENTS



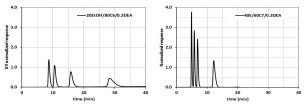
CHIRALPAK® AD

0.3%DEA in Mobile Phase Composition



BASELINE SEPARATION
R>1.5 and lower tr4

Solvent	ΔP (bar)	tr4 (min)	Critical pair	Critical Rij
20E/80C6	19	28.35	2,1	1.72
40E/60C7	31	12.12	2,1	1.71

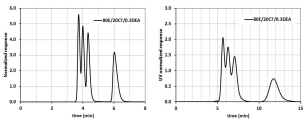


No good separation performances were obtained using n-propanol, iso-propanol and butanol in hexane and heptane mixtures.

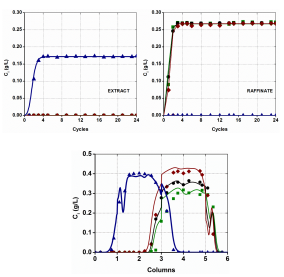
CHIRALPAK® AD

(1+2+3)/4 SEPARATION

Solvent	Column	Flow rate (mL/min)	ΔP (bar)	tr4 (min)	R4,3
80E/20C7	analytical	1	25	6.02	3.56
80E/20C7	SMB	5	36	11.73	2.69



(1+2+3)/4 SMB SEPARATION with C_i^F=2.0 g/L



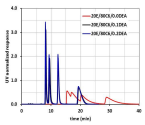
Experimental flow rates (mL/min) 24 cycles, T=24ºC	
Internal	External
Q_1^I = 21.7 ml/min	Q_E = 15.5 ml/min
Q_2^I = 9.8 ml/min	Q_F = 4.1 ml/min
Q_3^I = 13.9 ml/min	Q_R = 11.9 ml/min
Q_4^I = 6.2 ml/min	Q_S = 7.7 ml/min
	Q_{dil} = 6.2 ml/min

Outlet concentrations
$C_1^I = C_2^I = C_3^I = 0.27$ g/L
$C_4^I = 0.17$ g/L

Performance parameters
$RCX = 100\%$ $PUX = 100\%$
$SC = 9.6$ L/g
$PR = 0.65$ g/(L.h)

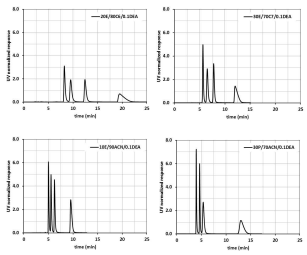
CHIRALPAK® IA

0.1%DEA in Mobile Phase Composition



BASELINE SEPARATION
R>1.5 and lower tr4

Solvent	ΔP (bar)	tr4 (min)	Critical pair	Critical Rij
20E/80C6	37	19.48	2,1	1.72
30E/70C7	53	12.02	2,1	1.89
10E/90ACN	33	9.53	2,1	1.57
30P/70ACN	39	13.02	3,2	1.64



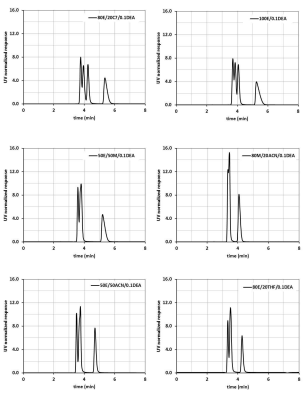
No good separation performances were obtained using mixtures with dichloromethane, tetrahydrofuran and ethyl acetate.

CHIRALPAK® IA

BETTER COMPOSITIONS FOR (1+2+3)/4 SEPARATION

STEREOISOMERS 1, 2 and 3 will coelute

Solvent	ΔP (bar)	tr4 (min)	R4,3
80E/20C7	87	5.35	3.38
100E	112	5.25	3.15
50E/50M	74	5.20	3.50
80M/20ACN	45	4.08	2.52
50E/50ACN	46	4.70	4.22
80E/20THF	84	4.28	3.80

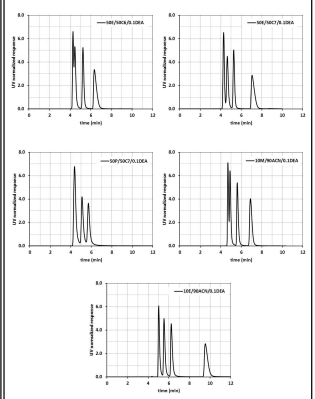


CHIRALPAK® IA

BETTER COMPOSITIONS FOR (1+2)/3/4 SEPARATION

STEREOISOMERS 1 and 2 will coelute

Solvent	ΔP (bar)	tr4 (min)	R3,2	R4,3
50E/50C6	61	6.33	2.40	2.44
50E/50C7	66	7.05	1.91	4.00
50P/50C7	79	5.72	1.95	1.65
10M/90ACN	31	6.88	2.80	3.66
10E/90ACN	33	9.53	1.65	6.00



CONCLUSIONS & FUTURE WORK

The use of mobile phases containing an alcohol is of utmost importance to obtain high solubility of the nadolol stereoisomers;
The presence of the basic modifier (DEA) is of utmost importance to obtain resolution (at least 0.1% DEA).

For Chiralpak® AD:

Baseline separation of all the 4 nadolol stereoisomers is obtained using Ethanol/Hexane and Ethanol/Heptane mobile phases;
The 40%Ethanol/60%Heptane/0.3%DEA is a better solvent composition for analytical chromatography: it allows the baseline separation of all the 4 nadolol stereoisomers with a lower retention time;
The 80%Ethanol/20%Heptane/0.3%DEA was proved to be a suitable solvent composition for the preparative separation of the more retained stereoisomer. Complete separation of this stereoisomer (PUX4=100%) was achieved using SMB technology.

For Chiralpak® IA:

Besides the use of Ethanol/Hydrocarbon mixtures, the use of Acetonitrile (with Ethanol or iso-Propanol) also allows baseline separation of all the 4 nadolol stereoisomers.
Good separation performance is obtained with 10%Ethanol/90%Acetonitrile/0.1%DEA with low retention times.
Different mobile phase compositions show potential to be used for the preparative (1+2+3)/4 and (1+2)/3/4 nadolol separations: this includes alcohol/hydrocarbon, alcohol/alcohol, alcohol/acetonitrile and alcohol/tetrahydrofuran mixtures.
Further tests will be carried out in the future to better explore all of these potential mobile phases for the preparative separation of nadolol stereoisomers using Chiralpak IA.

ACKNOWLEDGMENTS/FINANCIAL SUPPORT:

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