ChemPor 2023

14th International Chemical and Biological Engineering Conference

Book of Abstracts

Instituto Politécnico de Bragança | September 12-15

ORDEM DOS ENGENHEIROS

ipb INSTITUTO POLITÉCNICO DE BRAGANÇA

Programme

Time		Tuesday 12	Wednesday 13			Thursday 14			Friday 15		
08:00	09:00		*Registration*								
09:00	09:15		**Plenary lecture 1** Jarka Glassey - **ADG**			**Plenary lecture 3** Raquel Aires-Barros - **ADG**			**Plenary lecture 5** Rafael Luque - **ADG**		
09:15	09:30										
09:30	09:45										
09:45	10:00										
Session-Room			**S1-AAM**	**S1-ADG**	**S1-AP**	**S4-AAM**	**S4-ADG**	**S4-AP**	**S7-AAM**	**S7-ADG**	**S7-AP**
10:00	10:15		O EE-01	O BS-01	O RS-01	O BT-04	O MS-13	O RS-09	O BS-07	O RS-12	O BT-10
10:15	10:30		O EE-02		O RS-02	O BT-05	O MS-02	O RS-10	O BS-02	O RS-13	O BT-11
10:30	10:45		O EE-03	O BS-03	O RS-03	O BT-06	O MS-03	O RS-11	O BS-09	O RS-14	O BT-12
10:45	11:00		**Poster session 1** *Coffee-break Topics - EE IA MS and RS*			**Poster session 2** *Coffee-break Topics - BS BT and IM*			*Coffee-break*		
11:00	11:15										
11:15	11:30		**Keynote 1** - Juan F. Rodríguez - **AAM**			**Keynote 3** - Maria José Ferreira - **AAM**			**Keynote 5** - José Palomar - **AAM**		
11:30	11:45		**Keynote 2** - Luís Madeira - **ADG**			**Keynote 4** - Miguel Cerqueira - **ADG**			**Keynote 6** - Mara Freire - **ADG**		
Session-Room			**S2-AAM**	**S2-ADG**	**S2-AP**	**S5-AAM**	**S5-ADG**	**S5-AP**	**S8-AAM**	**S8-ADG**	**S8-AP**
11:45	12:00		O IM-01	O EE-04	O BT-01	O BT-07	O BS-04	O IM-04	O RS-15		O BS-10
12:00	12:15		O IM-02	O EE-05	O BT-02	O BT-08	O BS-05	O IM-05	O RS-16	O IM-10	O BS-11
12:15	12:30		O IM-03	O EE-06	O BT-03	O BT-09	O BS-06	O IM-06	O RS-17	O IM-11	O BS-12
12:30	14:00		*Lunch*								
Session-Room									**S9-AAM**	**S9-ADG**	**S9-AP**
14:00	14:15		**Plenary lecture 2** Joaquim Henrique Teles - **ADG**			**Plenary lecture 4** Margarida Costa Gomes - **ADG**			O IA - 05	O RS-18	O BT-13
14:15	14:30								O IA - 06	O RS-19	O BT-14
14:30	14:45								O IA - 07	O RS-20	O BT-15
14:45	15:00									O RS-21	O BT-16
Session-Room			**S3-AAM**	**S3-ADG**	**S3-AP**	**S6-AAM**	**S6-ADG**	**S6-AP**			
15:00	15:15		Sysadvance	Paralab	O EE-07	O IA - 01	O MS-04	O EE-13	O EE-19	O MS-10	O IM-12
15:15	15:30		O RS-04	Bondalti	O EE-08	O IA - 02	O MS-05	O EE-14	O EE-20	O MS-11	O IM-13
15:30	15:45		O RS-05	Bruker	O EE-09	O IA - 03	O MS-06	O EE-15	O EE-21		O IM-14
15:45	16:00		O RS-06	Prio	O EE-10	O IA - 04	O MS-07	O EE-16	**Awards ceremony - ADG**		
16:00	16:15	*Registration*	O RS-07	Cires	O EE-11	O IM-07	O MS-08	O EE-17	**CHEMPOR-2026**		
16:15	16:30		O RS-08	Hovione	O EE-12	O IM-08	O MS-09	O EE-18	**Closing session**		
16:30	16:45		**Poster session 1** *Coffee-break Topics - EE IA MS and RS*			**Poster session 2** *Coffee-break Topics - BS BT and IM*					
16:45	17:00										
17:00	17:15	**Opening ceremony - TMB**									
17:15	17:30	**Opening lecture**									
17:30	17:45	Jorge Calado									
17:45	18:00	**Honor session**									
18:00	19:00	Alírio Rodrigues				***Social program***					
19:00	19:30										
19:30	23:00					***Conference dinner***					

BS	Biorefinery and Sustainability
BT	Biotechnology
EE	Energy and Environment
IA	Industrial Applications
IM	Innovative Materials
MS	Modeling, Synthesis and Integration of Chemical Processes
RS	Reaction and Separation Processes

AAM	Auditório Alcínio Miguel
ADG	Auditório Dionísio Gonçalves
AP	Auditório Pequeno
TMB	Teatro Municipal de Bragança

Complete separation of nadolol stereoisomers by fixed-bed and simulated moving bed chromatography

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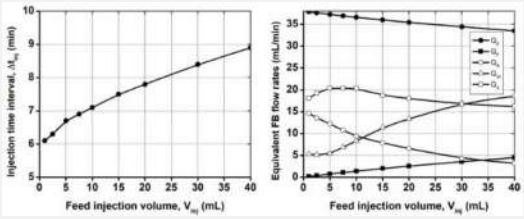

Effect of the feed injection volume in the injection time interval (left plot) and in the equivalent flow-rates (right plot) for the fixed-bed preparative separation of nadolol racemates.

This work deals with the identification of main experimental strategy for the complete separation of nadolol quaternary mixture into its pure four stereoisomers. Different chiral and achiral adsorbents, with different particle size diameters (5, 10 and 20 μm) as well as several solvents and solvent mixtures (aqueous and organic) are used. The selected global strategy is based on two main steps. The first step is the achiral separation of nadolol racemates (two pairs of enantiomers) by high pH reversed-phase preparative chromatography using C18 adsorbents. Then, the second step is based on two parallel binary chiral separations using Chiralpak IA adsorbents. It is important to notice that both first and second steps can be accomplished by fixed-bed and simulated moving bed (SMB) technologies. The theoretical and experimental results show that SMB technology presents higher preparative performance when compared to the "equivalent" preparative fixed-bed operation.

Highlights

• Strategies for complete preparative separation of nadolol chiral drug.
• Optimization of different solvent compositions using chiral and achiral adsorbents.
• Chiral separation by preparative SMB chromatography.

Introduction

Nadolol is a common prescribed pharmaceutical drug for the relieve of several cardiovascular diseases and represents a very interesting case-study of multicomponent chiral separation since it is composed by four stereoisomers, being two pairs of enantiomers. In this way, it introduces the possibility of alternative strategies, using different kind of preparative separation sequences and techniques, the use of different packings (chiral and achiral stationary phases), and the corresponding mobile phase optimization at both normal and reversed-phase modes.

When considering preparative and multicomponent separation, the complexity deeply increases by introducing the necessity of multi-step separation sequences (or a much more complex multi-region separation process), by opening the possibility to combine chiral and achiral stationary phases (when in presence of stereoisomers instead of just one pair of enantiomers) and to combine different separation techniques (fixed-bed and simulated moving bed (SMB) related processes). The design of the complete preparative separation of nadolol stereoisomers asks for a global experimental and simulation methodology considering both the characterization and optimization of each separation step and its sequences to achieve the four nadolol components pure. New strategies using combinations of achiral and chiral stationary phases and sequences of different separation techniques will be studied. Extensive experimental and simulation results for the complete separation of all the four nadolol stereoisomers using Chiralpak IA (chiral) and different Waters C18 (achiral) stationary phases will be presented.

Methods and materials

For the analytical measurements, an analytical Knauer HPLC was equipped with one Smartline 1050 pump, a 10 mL pump head and two detectors in series: a Smartline UV detector 2520 a polarimeter detector (Chiralser IBZ, Messtechnik, Germany). These measurements were performed using a Chiralpak IA column obtained from Daicel and a XBridge C18 column obtained from Waters. Both columns have the same analytical dimensions (250 mm L × 4.6 mm ID) and packed with 5 μm particle size materials. For the preparative measurements, a preparative Knauer HPLC system equipped with a Smartline UV detector 2520, two Smartline 1050 pumps with 50 mL pump heads, was used. Three different preparative columns (100 mm L × 20 mm ID) were used, a Chiralpak IA (particle size diameter 20 μm), a SiliaChrom XT18 and a XBridge C18 column (both with a particle size diameter of 10 μm). The binary SMB separations of nadolol racemates was performed on a laboratory-scale SMB unit built on the LSRE group, Faculty of Engineering, University of Porto. The SMB unit was operated using a [1-2-2-1] column configuration. The SMB unit was operated with 6 XBridge C18 columns for the binary separation of the two nadolol racemates (1+4)/(2+3) and 6 Chiralpak IA columns for the binary enantiomer separations (1/4) and (2/3). An Azura fixed-bed preparative commercial HPLC system obtained from Knauer was also used for the binary separation of nadolol racemates. This system was equipped with two preparative HPLC pumps P2.1L model with 250 mL/min pump heads, one UV detector UVD2.1L model and a unique Waters XBridge prep C18 column (30 mm ID x 250 mm L) with particle size diameter of 10 μm.

Results and discussion

An extensive set of experimental and simulation results will be presented (see Graphical Abstract, Figure 1, and Figure 2). Results will include the identification of the stereoisomers present in both nadolol racemates by means of using UV and polarimeter detectors in series. Then, a complete methodology developed during the last years by our group will be explained and applied to scale-up the separation process from analytical to preparative scales [1-4].

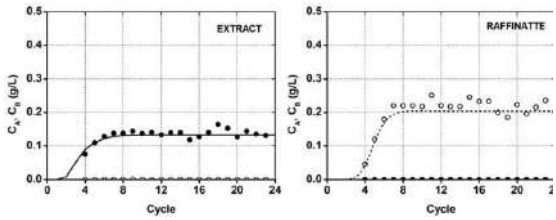

Figure 1. Experimental (points) and predicted (lines) transient evolution (24 full cycles) of the nadolol racemate concentrations in the extract and raffinate SMB outlet streams. Closed circles for the more retained racemate A, open circles for less retained racemate B, for a 2 g/L nadolol feed solution.

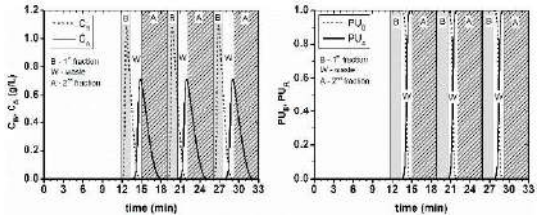

Figure 2. Simulated fixed-bed chromatograms of three consecutive pulses (left plot, dashed line for the less retained racemate B, solid line for more retained racemate A) and purities of B and A (right plot, dashed line for purity of B, solid line for purity of A) of a 9 g/L nadolol feed solution.

Conclusions

The selected and implemented methodology to perform the complete separation of the four nadolol stereoisomers is based on two main steps. The first step is an achiral preparative separation of the two racemates of nadolol (two pairs of enantiomers). The implementation of the first achiral step was done with the separation of nadolol racemates by high pH reversed-phase fixed-bed and simulated moving bed chromatography. Both systems use the Waters XBridge C18 adsorbent of 10 µm particle diameter. The second step is composed of two parallel preparative binary chiral separations of the racemates of nadolol, previously obtained on the first step.

For the first achiral step, an extensive study was carried to select the most promising achiral adsorbent and the more favorable solvent composition. The screening of the mobile phase composition elected the Waters XBridge C18 adsorbent and a 30:70:0.1 (v/v/v) ethanol:water:diethylamine solvent mixture to perform both FB and SMB preparative operations. For FB, using a feed concentration of 9 g/L of an equimolar mixture of the two nadolol racemates, both were recovered almost pure (at least 99.9%), with a global system productivity of 3.06 gfeed/(Lbed.hr) and a solvent consumption of 4.21 Lsolvent/gfeed. For SMB, the pilot unit's pressure drops limits imposed a maximum internal flow-rate of only 5 mL/min and, for a nadolol feed concentration of 2 g/L, both racemates were recovered 100% pure, with a system productivity of 0.13 gfeed/(Lbed.hr) and a solvent consumption of 6.19 Lsolvent/gfeed. Additional simulation results showed that a SMB preparative unit can perform the 9 g/L nadolol racemate separation with a system productivity of 3.61 gfeed/(Lbed.hr) and a solvent consumption of only 1.95 Lsolvent/gfeed using the same average internal flow-rate as in FB operation. Even better SMB productivities can still be obtained using the same feed or solvent flow-rates as in FB operation if the internal SMB flow-rates are allowed and not limited by the system pressure drop.

Concerning the second production step and for racemate A separation, a 25%methanol:75%acetonitrile solvent composition was elected, whereas for racemate B, a 5%methanol:95%acetonitrile was the selected composition. The experimental chiral separation of both nadolol racemates using SMB technology was carried out using the FlexSMB-LSRE unit. For racemate A and using a total feed concentration of 2 g/L, both nadolol stereoisomer (1 and 4) were recovered 100% pure in the outlet streams with a global system productivity of 1.81 g/(L.hr) and a solvent consumption for 2.47 L/g. For racemate B and using a total feed concentration of 2 g/L, both nadolol stereoisomer (2 and 3) were recovered 100% pure in the outlet streams with a global system productivity of 0.87 g/(L.hr) and a solvent consumption for 4.25 L/g.

Acknowledgements

The authors are grateful to the Foundation for Science and Technology (FCT, Portugal) for financial support through national funds FCT/MCTES (PIDDAC) to CIMO (UIDB/00690/2020, UIDP/00690/2020 and SusTEC (LA/P/0007/2021). National funding by FCT, Foundation for Science and Technology, through the individual research grant (SFRH/BD/137966/2018) of R. Arafah is also acknowledged.

References

[1] A. Ribeiro et al., Chirality, 25 (2013) 197-205.
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[4] R. Arafah et al., Separation and Purification Technology, 233 (2020) 116018.
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