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Enantioseparation of Gantofiban precursors on chiral stationary phases of the poly-(*N*-acryloyl amino acid derivative)-type

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Dedicated to Professor Dr Gottfried Blaschke on the occasion of his 65th birthday

Abstract

A separation strategy for the preparative enantioseparation of intermediates of the synthesis route towards the new antithrombotic drug Gantofiban is outlined. The selectivities of six different intermediates on a series of chiral stationary phases of the poly-[*N*-(meth-)acryloyl amino acid derivative]-type are determined. The separations are optimized with respect to high enantioselectivities and good solubilities in the mobile phase. For three optimized combinations of chiral stationary and mobile phases the separation parameters for a simulated moving bed-systems are determined.

Keywords: Chiral stationary phases; Preparative chromatography; Simulated moving bed-chromatography; Poly-[*N*-acryloyl amino acid ester]-chiral stationary phases; Chiraspher®

1. Introduction

Novel oxazolidinone-derivatives with a phenyl substitution in the 3-position have been found to inhibit the platelet aggregation in vivo and show a strong GPIIb/IIIa-antagonistic activity [1]. Different derivatives of the central oxazolidinone methyl unit with basic and acidic building blocks as N- and C-terminal residues, respectively, were synthesized to optimize the activity and bioavailability. From this series Gantofiban (Fig. 1) showed the highest activity [2].

All synthesized derivatives possess a chiral centre at the 5-position of the oxazolidinone-ring. The bioactivity is strongly depending on the stereo chemical configuration of the molecule, with a higher activity for the (R)-enantiomers [1]. Therefore, the need to synthesize stereochemically pure drug molecules and their synthesis intermediates was obvious. In addition, preparative chromatography was considered to be a valuable alternative in obtaining the single enantiomers, at

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least in quantities, which were sufficient for clinical trials.

Poly-[*N*-acryloyl amino acid esters] have been synthesized first by Blaschke in the early 1970s and have proven to be potent chiral stationary phases (CSP) for both analytical and preparative purposes [3]. By binding or coating the chiral polymers onto silica gel, stationary phases with higher stability and efficiency have been obtained [4,5] review in Ref. [6]. As it was known from previous studies those CSP exhibit excellent selectivity for chiral 5-membered rings [7], the separation of Gantofiban and its derivatives was tested first on CSP of this type. Good separations were found for most of the drug molecules and intermediates. The separation conditions were optimized and from the series of precursors three combinations of stationary and mobile phase were chosen for examining preparative separation conditions, which could be used for the production of these precursors by means of preparative simulated moving bed (SMB)-chromatography.

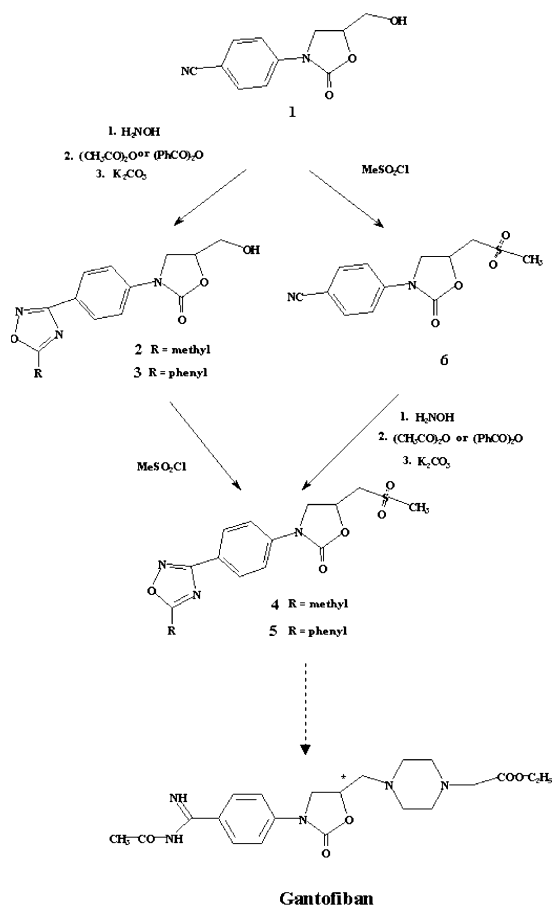


Fig. 1. Chemical structure and synthesis of Gantofiban.

2. Materials and methods

2.1. Analytical chromatography

All chromatograms were measured on a LaChrom-HPLC system consisting of a L-7110 HPLC-pump, a L-7400 UV-detector and a L-7300 column oven. The chromatograms were recorded with the software package HSM HPLC-Manager in combination with a D-7000 interface (Merck, Darmstadt, Germany). The detection wavelength was 254 nm. The mobile phases were all of gradient or reagent grade (LiChrosolve®, Merck, Darmstadt, Germany).

2.2. Chiral stationary phases

The chiral polymers were synthesized according to the procedure described in Refs. [4,5]. They were bonded to silica gel, which was either of 5 μm (LiChrospher Si 60, Merck Darmstadt, Germany) or 10 μm (Polygosil 100, Macherey-Nagel, Düren, Germany) particle size.

The sorbents were slurry packed into stainless steel columns of 250×4 mm dimensions by means of isopropanol as the slurry and compression liquid. The packing pressure was set to 300 bars.

2.3. Determination of solubilities

Twenty milligram of the compounds were carefully weighed into a vial. The solvent was added at room temperature in 100 μl portions, until a clear solution was obtained. The obtained solubility was regarded as a minimum solubility.

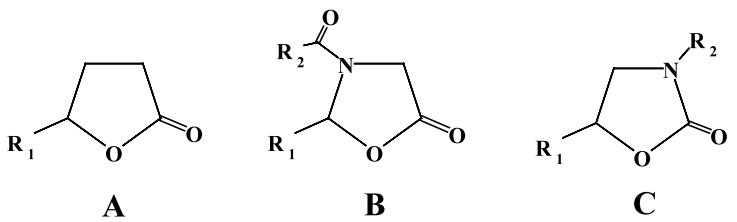


Fig. 2. Five-membered heterocycles separated on poly-[*N*-acrylolyl amino acid esters]: (A) γ-lactones Refs. [11,12], (B) oxazolidin-5-ones Refs. [7,13] and (C) Gantofiban.

2.4. Determination of isotherms and calculation of the SMB-starting parameters

The determination of the adsorption isotherms was achieved by the Elution by characteristic point (ECP)-method [8], which has been proven to be a quick and reliable method [9]. The chromatographic data were fitted by use of the software HELP from NOVA*SEP* (Nancy, France), which calculated the appropriate SMB-flow rates (basic model for the calculation is described in Ref. [10]).

3. Results and discussion

The synthetic route towards Gantofiban offers two possibilities (Fig. 1), wherein the chiral heterocyclic alcohol **1** is the key intermediate. This alcohol is synthesized by reacting 4-aminobenzonitrile with glycidol and a ring-closure of the resulting diol with diethyl carbonate. Complete synthesis reported in Ref. [2]. Alcohol **1** can be derivatized with hydroxylamine using route 1, followed by cyclisation as a protecting step with either acetic anhydride or benzoic anhydride. After cleavage of the ester with K_2CO_3 the intermediates **2** ($R = CH_3$) and **3** (R = Phenyl) are obtained. Mesylation of compounds **2** or **3** gives the reacting building blocks **4** or **5**, which can be further used to synthesize the final drug Gantofiban. The second route towards building blocks **4** or **5** includes a reversal of the synthetic steps. As a consequence alcohol **1** is mesylated first to form intermediate **6** and than the protection of the N-terminus is performed.

To control the synthesis and even more to find the intermediate, which offers highest productivity for a preparative chromatographic enantioseparation, compounds **1**–**6** were included into the screening of suitable CSP.

It was known from the literature that the CSP of the poly-[*N*-acryloyl phenylalanine ethyl ester]-type show high enantioselectivities for γ-lactones with a chiral substituent in the 5-position. Baseline enantioseparations have been reported for γ-lactones with different chain lengths [11,12] and chiral oxazolidin-5-ones [7,13]. Therefore enantioseparation of 5-membered rings with nitrogen atoms at the 3- or 4-position seemed possible. As the structural similarity of the above mentioned derivatives and the chiral central moiety of Gantofiban is obvious (Fig. 2) good chances for a successful enantioseparation on CSP of the poly-[*N*-acryloyl amino acid ester]-type were foreseen.

Blaschke has first used optically active acrylamides as CSP in a polymeric bead form in the early 1970s [14–16]. For gaining higher efficiencies and to avoid the swelling of the polymer the copolymerisation with vinyl-modified silica or the grafting onto silica were introduced by Blaschke, Fraenkel, Bröker and Kinkel in 1986 [17]. A silica based stationary phase with phenylalanine ethyl ester as the chiral selector was made commercially available in 1987 (Chiraspher®).

Acryl amide derivatives of homochiral amino acids are synthesized by means of acryloyl- or methacryloyl chloride. One out of several ways to copolymerize a silica/chiral polymer-composite is the radical polymerisation on the surface of diol-modified silica, which is derivatized with acryloyl groups. (For a review on other possible synthesis routes see Ref. [6]).

The chemistry of the chiral selectors is based either on amine or amino acid-derivatives (Fig. 3). Structure B in Fig. 3 shows the basic design of CSP with simple alkyl side chains, which have been

introduced as CSP very early [18]. Phenylethylamine, cyclohexylethylamine or menthylamine are derivatives widely used for the synthesis of such type of CSP.

The wide variety of amino acid derivatives offers the possibility to synthesize a manifold of CSP of structure A with different selectivities. Mainly four different groups can be introduced into the polymer. While R_3 can be either –H or $–CH_3$ a wide variety of different esters as R_2 can be used, the most common one being the ethyl ester. R_1 can be derivatized with the full range of natural and not naturally occurring amino acids or alcohols, especially the more bulky ones, e.g. menthylalcohol. Even dipeptide derivates can be successfully used.

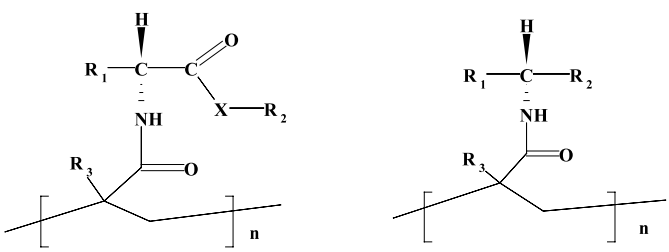
Beside the wide variety of different chiral selectors and the high efficiency of the silica-based sorbents, the described type of stationary phases offers two additional advantages:

By using the D- or L-form of the chiral selector the elution order of the analyte can be reversed. In analytical chromatography, the determination of traces of one enantiomer in a great excess of the other one is advantageous when the minor component is eluting in front of the major compound. In preparative chromatography, especially in its continuous SMB-form the eluent consumption and the dilution of the first eluting enantiomer is lower, resulting in lower purification costs.

The second advantage of the poly-[*N*-acryloyl amino acid]-derivatives bonded to silica is the excellent stability against a wide variety of different solvents. While the productivity of preparative enantioseparations is dominated by the solubility of the racemate in the mobile phase, a wide range of usable mobile phases is a great advantage in order to find a solvent, which offers high solubility and selectivity for the target compounds.

In this study, six different CSP of the poly-[*N*-(meth-) acryloyl amino acid derivative]-type have been used (CSP **I**–**VI**):

To determine the general selectivity of the CSP for the precursors of Gantofiban a generic approach was chosen first. The different intermediates **1**–**6** were dissolved in the mobile phase, which consisted of methyl-*tert*-butyl ether/tetrahydrofurane 75/25 (% v/v). The selection of this mobile phase ensures good retention behaviour of the analytes on the stationary phases even if the mobile phase composition is far from being optimal in terms of solubility for the ana-



A B

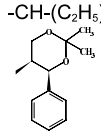
CSP		Type	R1	R2	X	R3
I	L-Phenylalanine ethyl ester	A	Ph-CH_2-	-C_2H_5	-O-	H-
II	L- Phenylalanine diethylamide	A	Ph-CH_2-	$(-C_2H_5)_2$	-N-	H.
III	L -Phenylglycine ethyl ester	A	Ph-	-C_2H_5	-O-	H-
IV	L- Cyclohexylethyl methacrylamide	B	Cyclohexyl-	-CH_3		CH_3-
V	L-Valine 3-pentyl amide	A	$(CH_3)_2$-CH-	-CH-$(C_2H_5)_2$	-NH-	CH_3-
VI	L-Leucin-(2,2-dimethyl-4S-phenyl-1,3-dioxan-5S-yl) amide	A	$(CH_3)_2$-CH_2-CH-		-NH-	CH_3-

Fig. 3. Structure of CSP of the poly-[*N*-(meth-)acryloyl amino acid derivative] type.

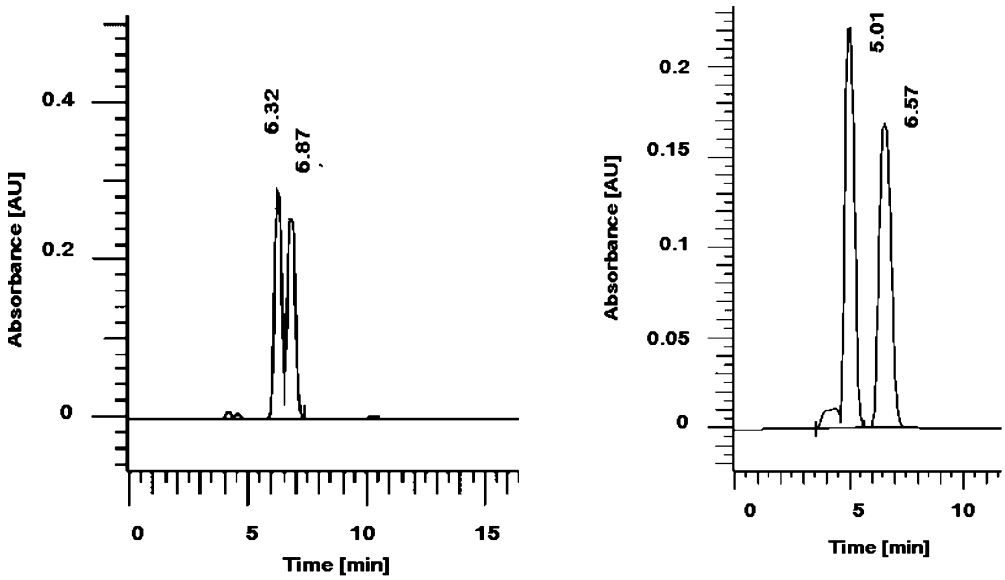


Fig. 4. Best analytical separations obtained on the six CSP (A) Separation of compound **6** on CSP **I** (Chiraspher®), mobile phase: methyl-*tert*-butyl ether/tetrahydrofurane 75/25 (% v/v), flow rate: 1.0 ml/min, detection: UV 254 nm. (B) Separation of compound **1** on CSP **VI**, mobile phase: methyl-*tert*-butyl ether/tetrahydrofurane 75/25 (% v/v), flow rate: 1.0 ml/min, detection: UV 254 nm.

lyte. To ensure that no compounds are fully adsorbed onto the column, a washing gradient to 100% THF was started after 20 min. The selectivities for the precursors **1**–**6** on the different CSP are summarized in Table 1.

As can be seen from Table 1 several CSP offer good enantioselectivities for the precursors of Gantofiban. The best separation on the poly-[*N*-acryloyl phenylalanine ethyl ester]-CSP is obtained for the mesylate intermediate **6** (Fig. 4A). The chiral stationary phase with the very bulky L-leucine (2,2-dimethyl-4S-phenyl-1,3-dioxane-5S-yl) amide-selector (CSP **VI**) separates all six intermediates with α-values > 1.4. As an example the separation of intermediate **1** is shown in Fig. 4B.

As mentioned before, the preparative separation of a given compound is mainly influenced by three parameters:

- the selectivity of the separation (or the resolution),
- the loading capacity of the stationary phase,
- the hydrodynamic properties of the sorbent (efficiency of column packing, column pressure drop, maximum linear flow rate).

One of the crucial parameters for a successful chromatographic enantioseparation is the solubility of the feed compound in the mobile phase, which is used for the separation. It can be seen from Table 1 that by using the mobile phase composition MTBE/THF 75/25 (% v/v) capacity factors k'_1 between 0.4 and 2 can be observed. These capacity factors can be ideally used for a preparative separation, in case the solubility in the mobile phase is higher than ≈ 10 g/l. However, this is not the case for this given mobile phase system. Therefore, the solubility for all six intermediates in solvents, which can be used as mobile phases, was examined. The criteria for the mobile phase selection were:

- wide range of different solvent strength,
- availability and usability in large volumes,
- moderate boiling points, to ensure an easy product recovery by solvent evaporation.

The solubility of the intermediates **1**–**6** in 13 solvents has been evaluated. Twenty milligram of each compound were exactly weighed and the solvent was added in 100 μl portions, until the compound was completely dissolved. No heat or

Table 1
Selectivity of the compounds **1**–**6** on different CSP

CSP	**1**			**2**			**3**			**4**			**5**			**6**		
	k'_1	α	R_S	k'_1	α	R_S	k'_1	α	R_S	k'_1	α	R_S	k'_1	α	R_S	k'_1	α	R_S
I	1.01			1.14			0.72			1.22	1.1	0.72	1.03	1.14	0.89	1.48	1.14	1.27
II	0.62			0.56			0.48			0.91			0.61			0.8	1.08	0.46
III	0.8			0.68			0.58			1.49			0.95			1.46		
IV	1.36			0.9			0.7			0.77			0.49			1.25		
V	0.88	1.16	0.73	0.45			0.36			0.24	1.22	0.51	0.19			0.56	1.4	0.50
VI	0.91	1.66	2.02	0.78	1.62	1.49	0.48	1.85	1.56	1.18	1.71	2.35	0.81	2.0	2.24	2.1	1.39	1.51

ultrasound was applied to enforce the dissolution. By using this method no exact determination of the solubility is possible but the solubility can be obtained with a certain safety margin, which is necessary for a preparative chromatographic separation. The solubility values are given in Table 2 as minimum or maximum values.

The solvent strength of a mobile phase influences not only the retention behaviour but also the separation efficiency or even the selectivity. The relative polarity ε^0, where the value for pentane is defined to be zero, gives the elution strength for different types of solvents [19]. Good solubilities for the intermediates were only obtained in solvents with a polarity ε^0 between 0.4 and 0.6. All compounds are only poorly soluble in very apolar solvents like *n*-heptane or cyclohexane. On the other hand, very polar solvents like alcohols also only poorly dissolve most of the compounds.

Therefore, all further separation attempts were concentrated on the range of medium polar solvents. Those solvents have to be mixed with apolar solvents to assure certain retention on the CSP. A compromise had to be found, where the compounds show good enantioselectivity ($\alpha > 1.2$), have a moderate retention ($0.8 < k'_1 < 5.0$) and a good solubility (> 5 g/l). To obtain those solubilities in mixed solvents, the solubility in the pure polar compound should be > 15 mg/ml. As none of the examined solvents assures those high solubilities for the compounds **3** and **4**, these compounds were no longer taken into account for a preparative separation.

The following combinations could be figured out for further optimisation of the separation.

Compound	CSP	Mobile phase
1	**VI**	*n*-heptane/ethanol
1	**VI**	*n*-heptane/THF
2	**VI**	*n*-heptane/dioxane
5	**I**	*n*-heptane/ dichloromethane
5	**I**	*n*-heptane/dioxane
6	**VI**	*n*-heptane/methyl acetate
6	**I**	*n*-heptane/methyl acetate

Each of the combinations had to be optimized separately to fulfil the above-mentioned conditions. The results of the optimisation with different mobile phase compositions are shown in Fig. 5. For compound **6** on poly-[*N*-acryloyl L-phenylalanine ethyl ester] (CSP **I**) the composition of the mobile phase *n*-heptane/methyl acetate was varied from 70% methyl acetate to 50% methyl acetate. As can be seen from Fig. 8 only at 50% methyl acetate the retention and the selectivity are high enough for a preparative separation.

Table 2
Solubility (mg/ml) of the compounds **1–6** in different solvents

Solvent	Polarity ε^0	Boiling point (°C)	**1**	**2**	**3**	**4**	**5**	**6**
n-Heptane	0.01	98	<1	<1	<1	<1	<1	<1
Cyclohexane	0.04	81	<1	<1	<1	<1	<1	<1
Methyl-*tert*-butyl ether	0.2	55	<1	<1	<1	<1	<1	<1
Di-isopropyl-ether	0.28	70	<1	<1	<1	<1	<1	<1
Dichloromethane	0.42	40	>7	>5	>2	>6	>30	>7
Ethyl-methyl-ketene	0.51	80	>4	>10	>4	>4	>5	>5
Dioxane	0.56	101	>23	>23	>5	>5	>25	>7
Acetone	0.56	56	>50	>24	>5	>9	>20	>30
Tetrahydrofurane	0.57	66	>50	>20	>10	>4	>24	>8
Ethyl acetate	0.58	77	>13	>6	>2	>2	>7	>3
Methyl acetate	0.6	57	>15	>9	>2	>4	>11	>8
Ethanol	0.88	79	>15	>4	<1	<1	<1	<1
Methanol	0.95	65	>4	>2	<1	<1	<1	<1

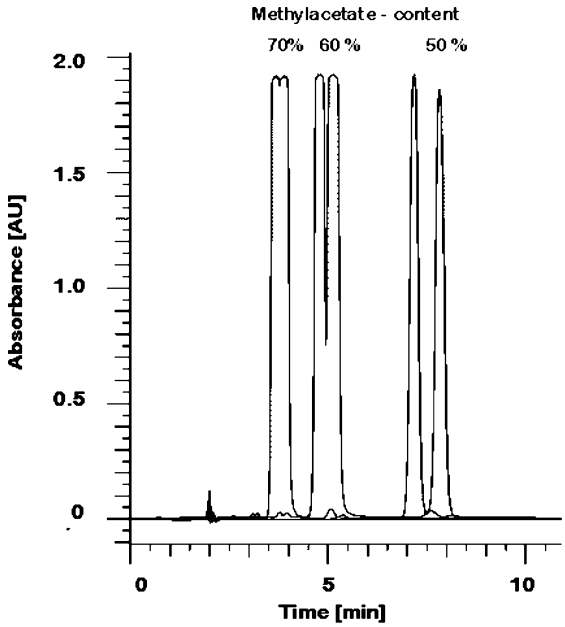


Fig. 5. Variation of methyl acetate-content on CSP **I** (Chiraspher®) for compound **6**, mobile phase: *n*-heptane/methyl acetate, flow rate: 1.0 ml/min, detection: UV 254 nm.

From the combinations outlined above, three have been found worth to determine their related SMB-parameters thoroughly. All of them are based on the separation of either compound **1** or **6** on CSP **VI**. The details of the separations are given in Table 3. Fig. 6 shows the corresponding chromatograms. Fig. 6B and C show chromatograms, optimized for preparative chromatography. However, baseline separation is no longer achieved. This compromise is necessary to ensure a good solubility and retention behaviour. Nevertheless, also good baseline separations were observed during the optimisation study, which can be used for analytical purposes, as it is shown in Fig. 6D for compound **5** on CSP **I**. Unfortunately, this separation cannot be used for a preparative separation due to the limited solubility.

For determining the correct setting of the flow parameters and the switching time for an SMB-system, it is necessary to determine the adsorption isotherms of the compounds to be separated. The quickest and easiest method to determine the isotherms is the ECP-method. This method can be applied, when the column efficiency is high enough [8]. To determine the isotherm it is necessary to inject a small amount of the analyte to obtain a chromatogram in the linear range of the adsorption isotherm. In addition four to five injections with increasing amounts of the analytes have to be recorded. From the breakthrough of the adsorptive front the isotherm can be calculated by means of a simulation software (in this case, HELP from NOVA*SEP*). The chromatograms of the injections of increasing amounts are overlaid in Fig. 7. The shift in retention time for both enantiomers can be clearly seen. For the three different combinations of intermediate/chiral stationary phase and mobile phase given in Table 4, the isotherms have been determined by using this approach.

The continuous separation method of SMB-chromatography has been proven to be a very efficient method for the isolation of enantiomers in large scale [20,21]. The principle of SMB-chromatography is shown in Fig. 8: a series of columns is connected to form a circle. Between each two columns valves are integrated, which can open or close solvent lines connected to four pumps. Two of the pumps are feeding the racemate and fresh eluent into the system, while the two other pumps withdraw continuously the less

Table 3
Combination of analytes and CSP

Compound	CSP	Mobile phase	Comp.	Solubility (g/l)	Selectivity α	Retention k'_1	Resolution R_S
1	**VI**	*n*-heptane/ethanol	55/45	4.8	1.35	1.3	1.49
6	**VI**	*n*-heptane/methyl acetate	50/50	1.0	1.16	3.5	1.12
1	**VI**	*n*-heptane/THF	50/50	5.25	1.18	4.5	0.83

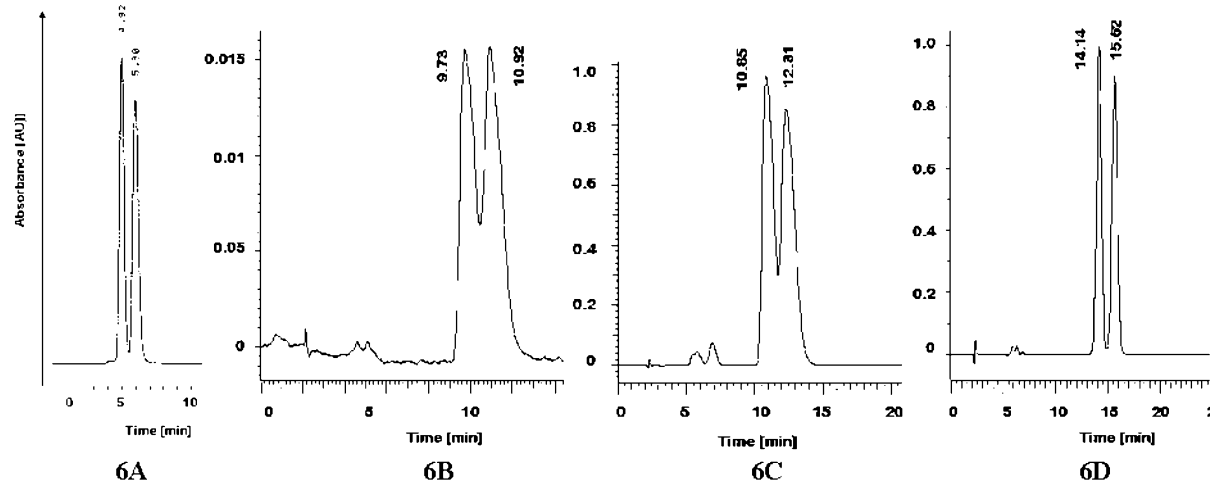


Fig. 6. Separations for which the SMB-parameters have been determined (A) Separation of compound **1** on CSP **VI**, mobile phase: *n*-heptane/ethanol 55/45 (% v/v), flow rate: 1.0 ml/min, detection: UV 254 nm. (B) Separation of compound **6** on CSP **VI**, mobile phase: *n*-heptane/methyl acetate 50/50 (% v/v), flow rate: 1.0 ml/min, detection: UV 254 nm. (C) Separation of compound **1** on CSP **VI**, mobile phase: *n*-heptane/THF 50/50 (% v/v), flow rate: 1.0 ml/min, detection: UV 254 nm. (D) Separation of compound **5** on CSP **I** (Chiraspher®), mobile phase: *n*-heptane/dioxane 60/40 (% v/v), flow rate: 1.0 ml/min, detection: UV 254 nm.

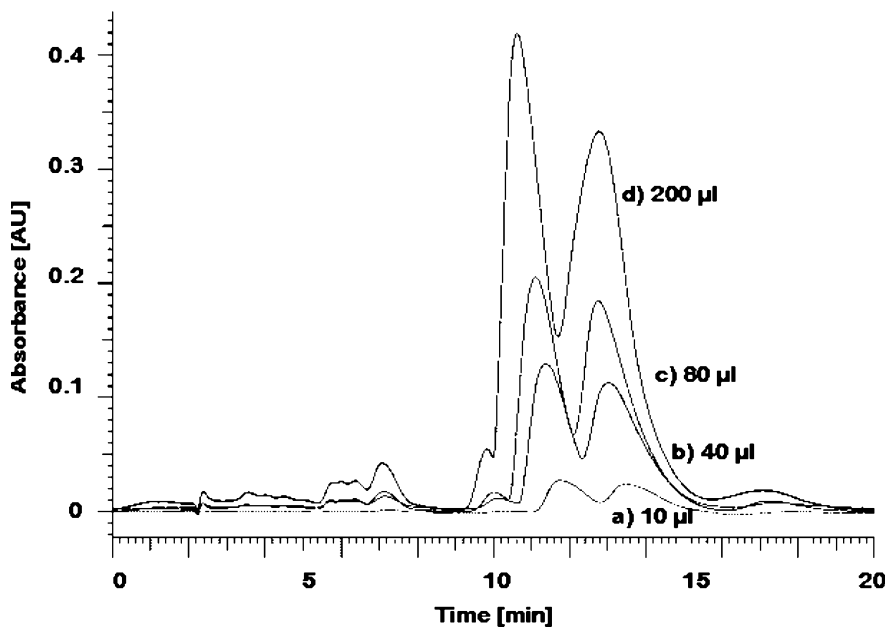


Fig. 7. Injection of increasing amounts of compound **1** on CSP **VI**, mobile phase: *n*-heptane/THF 50/50 (% v/v), flow rate: 1.0 ml/min, detection: UV 254 nm, feed concentration: 5.25 mg/ml, injection amount: (a) 10 µl (b) 40 µl (c) 80 µl and (d) 200 µl.

retained product (raffinate) and the more retained product (extract). A fifth pump is moving the mobile phase through the columns. At a given time, the valves are opened only at one specific position for each of the four lines. After the switching time, the valve positions are shifted for

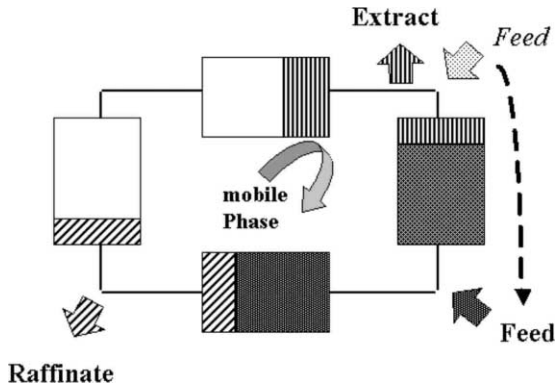


Fig. 8. Principle of SMB-chromatography.

one position in the direction of the mobile phase flow. This shift simulates the counter current movement of the stationary phase.

The advantages of SMB-chromatography are apart from its continuous operation the lower efficiency requirements for the stationary phases, the higher productivity and lower solvent consumption.

A given SMB-system is characterized by the five pump flow rates and the switching time. The performance of an SMB-system is given by the throughput (amount product separated per day on a given system), the productivity (amount product separated per day and amount stationary phase) and the eluent consumption (litre eluent consumed per g product).

The SMB-flow rates and the performance parameters are shown for the three different combinations in Table 4.

It can be seen from Table 4 that the throughput and the productivity are the highest for system 3 with a throughput of 120 g of enantiomer on an eight-column lab-scale SMB-system with 50 mm column diameter. The specific productivity for this system is determined with 103 g enantiomer per day and kg chiral stationary phase. Decreasing the purity requirements for the chromatographic enantiomer separation to 97% followed by increasing the product purity afterwards by means of crystallisation, can further increase the productivity. Another advantage of system 3 stems from the fact that compound **1** is the product, which is the key intermediate in the synthesis scheme. When this chiral key intermediate is separated into its pure enantiomers only

Table 4
Parameters and performance of the different SMB-systems

Parameter	System 1	System 2	System 3	System 3A
Compound	**1**	**6**	**1**	**1**
CSP	**VI**	**VI**	**VI**	**VI**
Mobile phase	*n*-heptane/ethanol	*n*-heptane/methyl acetate	*n*-heptane/THF	*n*-heptane/THF
Composition (% v/v)	55/45	50/50	50/50	50/50
Feed concentration (g/l)	4.8	1.0	5.25	5.25
Number of columns	8	8	12	8
Column length (mm)	100	100	100	100
Column diameter (mm)	50	50	50	50
Amount of CSP (kg)	0.785	0.785	1.178	0.785
Purity of products	>99%	>99%	>99%	>97.5%
Flowrate recycling (ml/min)	420.2	936.0	960.6	960.6
Flowrate feed (ml/min)	23.1	45.5	45.3	45.3
Flowrate eluent (ml/min)	104.6	185.4	225.0	225.0
Flowrate raffinate (ml/min)	39.7	88.7	98.5	98.5
Flowrate extract (ml/min)	88.1	142.3	171.6	171.6
Switching time (min)	0.91	4.57	5.56	5.56
Throughput (g enantiomer/d)	71.85	23.31	121.33	121.33
Productivity (g enantiomer/d and kg CSP)	91.53	29.70	103.04	154.56
Eluent consumption (l/g enantiomer)	2.56	14.26	3.21	3.21

50% of the total amount of compound has to be further transformed into enantiopure Gantofiban. This results in substantial savings in educt costs and equipment size.

4. Conclusions

CSP of the poly-[*N*-(meth-) acryloyl amino acid derivative]-type have been shown to be very useful in the separation of chiral intermediates of drug substances. The high variability of different chiral selectors allows the systematic screening for optimal preparative separation conditions. Due to the high chemical stability of these stationary phases, it is possible to use a wide variety of solvents with different polarities and solvent characteristics.

Within the route towards a final drug compound all chiral intermediates have to be taken into account for a preparative enantioseparation. As it was shown in this study the productivities and in conjunction with this the production costs can vary significantly from one intermediate to another. For the precursors of Gantofiban it turned out that the alcohol intermediate **1** can be separated with the highest productivity, reducing the amount, which has to be carried on during the synthesis at the earliest possible stage.

Nevertheless, the productivity of the optimized separation is low compared to other separations performed in our labs or described in literature. While the best system in this study separates intermediate **1** with a productivity of 150 g enantiomer per day and kg CSP, other separations have been reported with productivities up to 1000 g enantiomer per day and kg CSP [20,21]. As a rule of thumb, the productivity has to reach at least 400 g enantiomer per d and kg CSP to ensure an economic enantioseparation in production scale. Despite this fact, the separation of enantiomers by means of SMB-chromatography is a very quick and efficient tool to produce the first kg-amounts of developmental drug compounds with high purities and within reasonable time, which is essential to nowadays pharmaceutical research.

Furthermore, as the high molecular diversity of CSP based on polymeric amino acid derivatives offers one of the most flexible approaches for chromatographic enantioseparations, a further increase of the productivity for the Gantofiban precursors can be expected.

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