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Effect of (+) or (−) camphorsulfonic acid additives to the mobile phase on enantioseparations of some basic drugs on a Chiralcel OD column

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Dedicated to the memory of Danuta Sybilska.

Abstract

This paper describes the modification of Chiralcel OD column properties by adsorption of (+) or (−) camphorsulfonic acids (CSAs) used as additives to the mobile phase. The effects on retention, selectivity and efficiency, of adsorption of (+) and (−) CSAs on a Chiralcel OD column were examined. Racemic anti-histamines, anti-malarial and anti-fungal drugs, namely doxylamine, miconazole, sulconazole, hydroxyzine, homochlorcyclizine, methoxypheniramine, cyclopentolate and ephedrine were investigated as chiral tested compounds. All the studied drugs have an amino nitrogen atom in their structure. Only the enantioseparation of ephedrine enantiomers with CSAs alone was studied on the Nucleosil stationary phase, and these results were compared with the results obtained on the Chiralcel OD phase. A new dynamically generated stationary phase, with very good enantioseparation ability towards the studied compounds, was obtained by the adsorption of (−) CSA on the Chiralcel OD column.

Keywords: Chiralcel OD; Camphorsulfonic acid; Mobile phase additives; Basic drugs

1. Introduction

When building a new HPLC method for direct separation of enantiomeric drugs, it is usually preferable to use a chiral stationary phase (CSP), due to the simplicity of operation. There are various types of CSPs available. Among them, cellulose and amylose based CSPs have been proved to be quite versatile [1,2]. It is generally believed that the polar ester and carbamate groups are the main adsorbing sites on cellulose and amylose derivative columns. These groups can interact with a solute via hydrogen bonding, dipole–dipole interaction, and charge transfer complex (π–π) formation. Booth and Wainer [3] have found that chiral recognition seems to be a function of the fitting of the asymmetric portion of the solute in a chiral groove or channel of the CSP, and that this fit has rigid steric requirements. Whatever the type of interaction involved, one always has to consider that the mobile phase additives are a dynamic part of the system, capable of interacting with both the enantiomers and the CSP.

The effect of the mobile phase additives may be attributed to various possible mechanisms, for example: the additives may activate or block interaction between the solute and the stationary phase, they could interact with the solute in the mobile phase, for example to form an "ion-pair" complex with the analyte, which may have different selectivity in interacting with the stationary phase, or the additives may dynamically generate a new stationary phase. This means that the additives can change not only the retention of the enantiomers but also their separation.

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Commercially available cellulose and amylose based columns have been successfully applied in many practical procedures. The fact that their properties may be strongly influenced by mobile phase additives has also been well recognized and used to advantage in practice. However, the mechanism of chromatographic processes occurring on these stationary phases still remains open to discussion.

Amine and acidic mobile phase additives are often used to minimize peak broadening arising from unwanted interaction between polar solutes and the stationary phase [4]. Ye et al. [5,6] reported that the use of acidic and amine mobile phase additives allows the chiral separation of underivatized amino acids on a common amylosic column.

The small amount of water present in normal phase systems with Chiralcel OD and Chiralpak AD columns was found to be critical and indispensable to obtain chiral separation of some drugs [7,8].

In the present paper we would like to gain an insight into the mechanism of stationary phase action by checking how the addition of (+) and (−) CSAs, which are very often used as ion pair reagents to enantioseparation by crystallization, changes the enantioseparation of basic drugs on a Chiralcel OD column. We examined the effects of small additions of acetic acid (AcOH), or (+) or (−) CSAs together with water to the mobile phase, on retention, selectivity and efficiency of the column. To the best of our knowledge, no studies on how adsorption properties of the polysaccharides stationary phase may be influenced by enantiomeric additives have been reported to date.

Racemic anti-histamines, anti-malarial and anti-fungal drugs, namely doxylamine, miconazole, sulconazole, hydroxyzine, homochlorcyclizine, methoxypheniramine, cyclopentolate and ephedrine were investigated as chiral tested compounds. All the studied drugs have an amino nitrogen atom in their structure. In contrast, benzoin taken as the reference substance does not possess any.

2. Experimental

2.1. Materials

The *n*-hexane was HPLC grade and the 2-propanol (IPA) was of analytical reagent grade. All the other reagents were at least of analytical grade and were used as received. The (+) and (−) enantiomers of ephedrine and (+) and (−) camphorsulfonic acids (CSAs) were supplied by Fluka (Buchs, Switzerland), the rest of the studied compounds were supplied by Sigma–Aldrich (Dorset, UK).

2.2. Apparatus and procedures

Chromatographic experiments were performed using a Waters (Vienna, Austria) pump Model 590 and UV–vis detector Model 490, a 5 μl loop Rheodyne type injector. Nucleosil 100 –7 (Macherey-Nagel Duren) and Chiralcel OD (Daicel) (25 cm × 0.46 cm) columns were used.

The samples of investigated drugs were dissolved in the mobile phase for System 0. The structural formulas of the investigated drugs are collected in Table 1.

All the studied compounds were detected at 220 nm.

The mobile phases used for enantioseparation on the new Chiralcel OD column were as follows: hexane and 2-propanol (IPA) (80:20, v/v)—System 0, and with additives: water (0.2%)—System I, water (0.2%) with acetic acid AcOH (0.1%)—System II, and water (0.2%) with (+) or (−) CSAs (1.2 mM)—Systems III and IV, respectively. The mobile phase for the Nucleosil column was composed of hexane and 2-propanol (IPA) (80:20, v/v) and additives: water (0.2%) and (−) CSA (1.2 mM) or (−) CSA alone, without water.

The flow rate for both columns was 0.8 ml/min. The Nucleosil column was stabilized by the passing of the mobile phase solution for 3 h. The Chiralcel OD column was stabilized by the passing of the mobile phase solution for 1 h for System 0, I and II, and for 3 h for Systems III and IV prior to the chromatographic measurements.

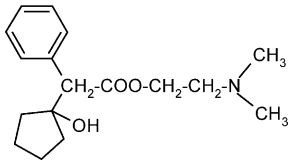
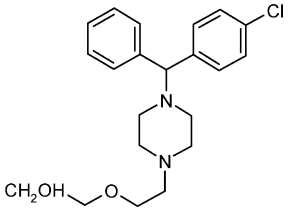
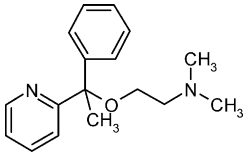
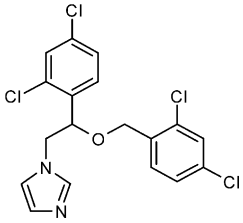
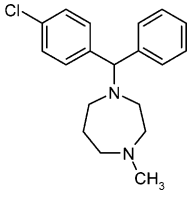
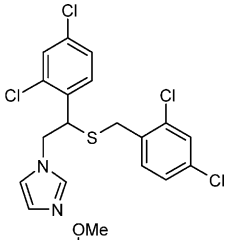
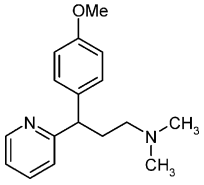
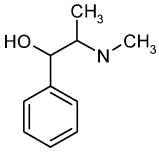
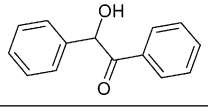
To remove the additives from the Chiralcel OD column between changes of eluent, the columns were washed extensively: 1 h with hexane:IPA (80:20, v/v) for System I, 2 h with IPA for System II and 1 h with IPA and 4 h with a mixture of IPA:water 4:1 and then 2 h with IPA for System III and IV [9]. After the washing procedure, the performance of the Chiralcel OD column was controlled with the mobile phase as in System 0.

All chromatographic measurements were performed at ambient temperature in an air-conditioned room (23 °C).

The elution order of the enantiomers was determined only for (+) and (−) enantiomers of ephedrine because of the lack of the single enantiomers of the other studied compounds.

The adsorption of the CSAs on the Chiralcel OD column were studied in a separate experiments. For the various hexane IPA mixtures the elution of the acids from the column was not observed; even for pure IPA as the eluent, the retention time of both acids was longer than 180 min. To obtain more information about adsorption of the CSA on that column, frontal analysis was applied in the next experiment. The eluent was composed of 10^{-2} M (+) CSA in IPA. To avoid high pressure, the flow rate was 0.3 ml/min. The dead volume for this flow was about 15 min; the column "breakthrough" occurs after 30 min. To control chromatographic parameters of the column treated in this way, first the whole chromatographic system was washed by IPA for 3 h and then the retention of hydroxyzine and homochlorocyclozine was checked in the eluent consisting of a hexane:IPA (80:20, v/v) mixture. The retention time for both compounds was longer than 50 min (for the newly purchased column the retention for these compounds was very short—see Table 3). To return to the original behavior of the

Table 1
Structure of drugs studied

Cyclopentolate	
Hydroxyzine	
Doxylamine	
Miconazole	
Homochlorcyclizine	
Sulconazole	
Methoxypheniramine	
Ephedrine	
Benzoin	

column, the washing procedure as for systems III and IV was used.

3. Results and discussion

In our experiment we studied five different chromatographic systems using the newly purchased Chiralcel OD column and various mobile phase compositions. The results obtained are presented in Table 2 and in Figs. 1–4.

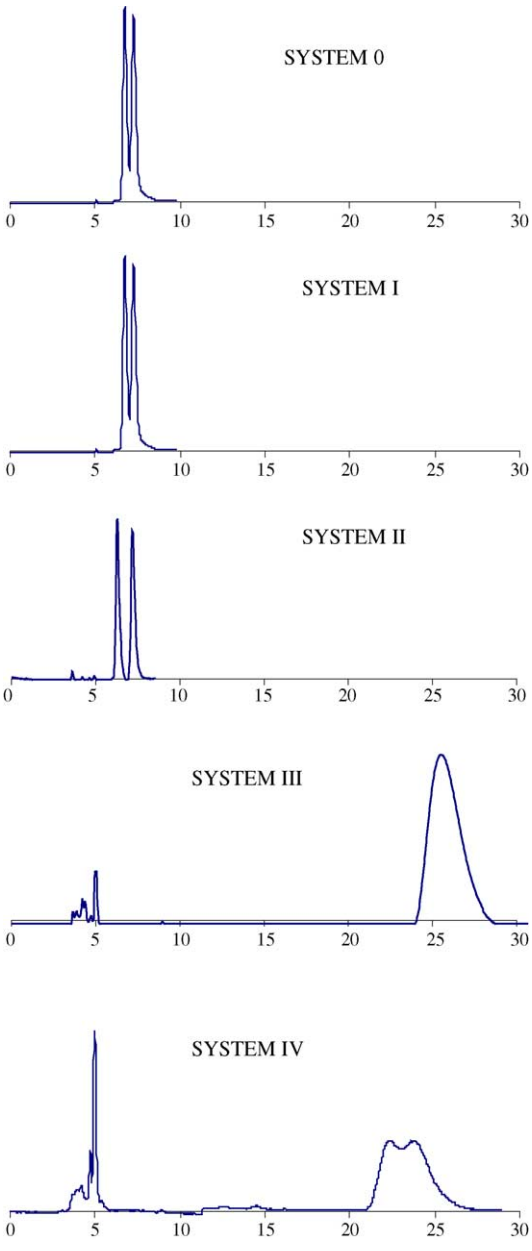
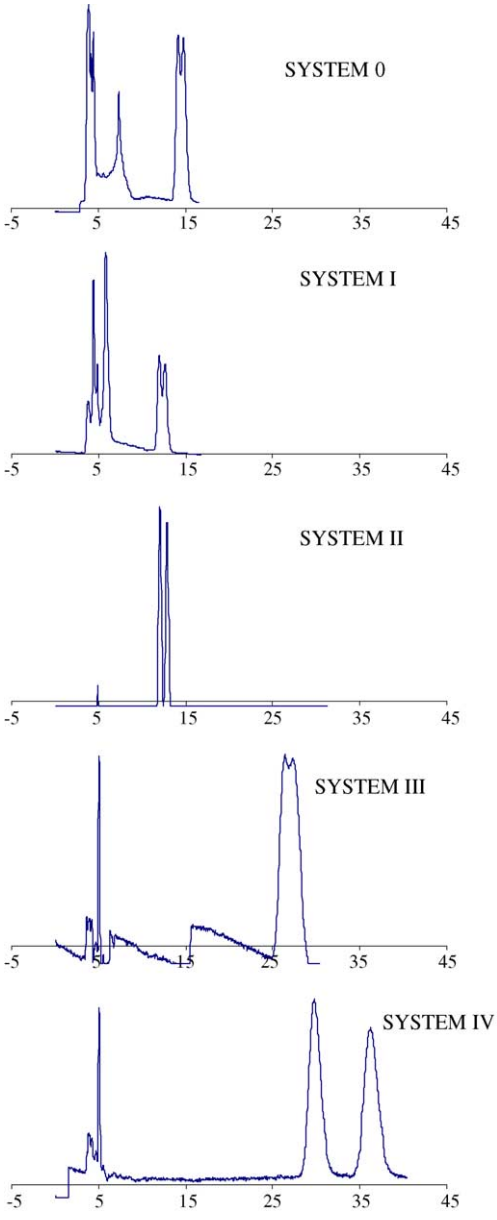


Fig. 1. Chromatograms of hydroxyzine obtained on Chiracel OD column with various mobile phase composition. Mobile phase hexane:IPA (80:20, v/v)—System 0 and with additives: water (0.2%)—System I, water (0.2%) with AcOH (0.1%)—System II, water (0.2%) with (+) CSA (1.2 mM)—System III and water (0.2%) with (−) CSAs (1.2 mM)—System IV.

Table 2
Chromatographic parameters of the investigated compounds depending on the composition of the mobile phase

Compound	System 0 (20% IPA)		System I (20% IPA + H_2O)		System II (20% IPA + H_2O and AcOH)		System III (20% IPA + H_2O and (+) CSA)		System IVA (20% IPA + H_2O (−) CSA)		System IVB (20% IPA + H_2O (−) CSA)	
	k_1 (α)	k_2 (Rs)	k_1 (α)	k_2 (Rs)	k_1 (α)	k_2 (Rs)	k_1 (α)	k_2 (Rs)	k_1 (α)	k_2 (Rs)	k_1 (α)	k_2 (Rs)
Cyclopentolate	0.7 (1.00)	0.7	0.5 (1.20)	0.6 (0.4)	0.9 (1.22)	1.1 (0.4)	3.1 (1.33)	4.1 (1.4)	3.6 (1.61)	5.8 (2.4)		
Hydroxyzine	0.8 (1.20)	1.0 (1.1)	0.6 (1.25)	0.8 (1.3)	0.7 (1.40)	0.9 (1.9)	5.9 (1.00)	5.9	5.1 (1.08)	5.4 (0.4)	4.7 (1.09)	5.2 (0.4)
Doxylamine	0.4 (1.13)	0.5 (0.5)	0.4 (1.31)	0.6 (0.6)	0.65 (1.08)	0.7 (0.3)	23.6 (1.07)	25.3 (0.4)	16.3 (1.30)	21.1 (1.7)		
Miconazole	2.8 (1.06)	3.0 (0.5)	2.2 (1.07)	2.4 (0.5)	2.2 (1.11)	2.5 (1.1)	6.1 (1.04)	6.4 (0.4)	7.0 (1.25)	8.8 (1.9)	6.7 (1.24)	8.3 (2.08)
Homochlorcyclozine	0.3 (1.00)	0.3	0.2 (1.22)	0.3 (0.5)	0.7 (1.24)	0.8 (0.7)	6.0 (1.12)	6.7 (0.7)	6.4 (1.13)	7.2 (0.6)	6.4 (1.12)	7.1 (0.6)
Sulconazole	6.1 (1.31)	8.0 (3.2)	5.2 (1.23)	6.4 (2.4)	5.2 (1.24)	6.4 (2.7)	7.8 (1.06)	8.3 (0.5)	9.1 (1.19)	10.8 (1.6)	7.9 (1.19)	9.4 (1.6)
Methoxypheniramine	0.5 (1.21)	0.6 (0.7)	0.4 (1.19)	0.5 (0.6)	0.7 (1.00)	0.7	1.9 (1.13)	2.2 (1.1)	2.5 (1.20)	3.0 (1.7)	2.4 (1.19)	2.9 (1.6)
Ephedrine	0.8 (1.32)	1.0 (0.8)	0.6 (1.27)	0.8 (0.8)	0.7 (1.08)	0.7 (0.3)	1.4 (1.24)	1.7 (1.7)	1.6 (2.18)	3.4 (6.3)	1.5 (2.15)	3.2 (6.1)
Benzoin	1.5 (1.52)	2.3 (5.1)	1.3 (1.55)	2.1 (5.1)	1.3 (1.55)	2.1 (5.1)	1.3 (1.6)	2.2 (5.1)	1.3 (1.55)	2.1 (5.1)	1.3 (1.55)	2.1 (5.1)

Chromatographic conditions: column Chiracel OD; flow rate 0.8 ml/min, detection 220 nm; mobile phase: hexane:IPA (80:20, v/v) System 0 and with additives: System I—0.2% water; System II—0.2% water and 0.1% AcOH; System III—0.2% water and (+) CSA; System IV—0.2% water and (−) CSA. (A) the first experiment and (B) experiment repeated after washing procedure.



ig. 2. Chromatograms of miconazole obtained on Chiracel OD column with various mobile phase composition. Mobile phase hexane:IPA (80:20, v/v) System 0 and with additives: water (0.2g) System I, water (0.2g) with AcOH (0.1g) System II, water (0.2g) with (x) CSA (1.2 mM) System III and water (0.2g) with (−) CSAs (1.2 mM)—System IV.

3.1. Mobile phase effect on the retention, enantioselectivity and efficiency obtained on the Chiralcel OD column

For the reference compound, benzoin, the retention, enantioselectivity and efficiency of the column was not dependent on the mobile phase composition, see Table 2. The results for the other studied substances depending on the mobile phase composition are discussed below.

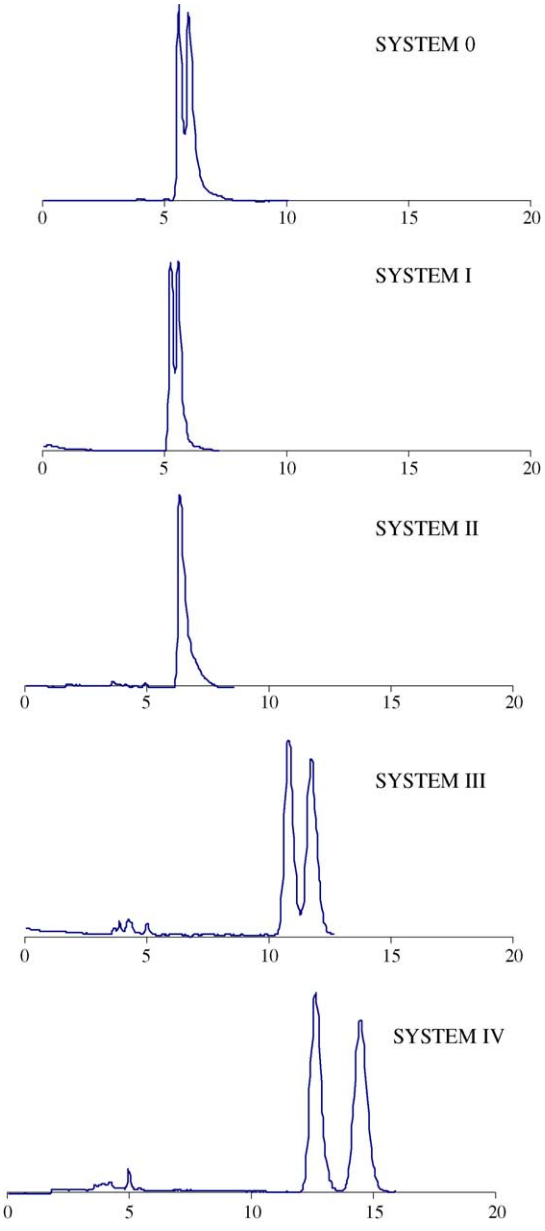


Fig. 3. Chromatograms of methoxypheniramine obtained on Chiracel OD column with various mobile phase composition. Mobile phase hexane:IPA (80:20, v/v)—System 0 and with additives: water (0.2%)—System I, water (0.2%) with AcOH (0.1%)—System II, water (0.2%) with (+) CSA (1.2 mM)—System III and water (0.2%) with (−) CSAs (1.2 mM)—System IV.

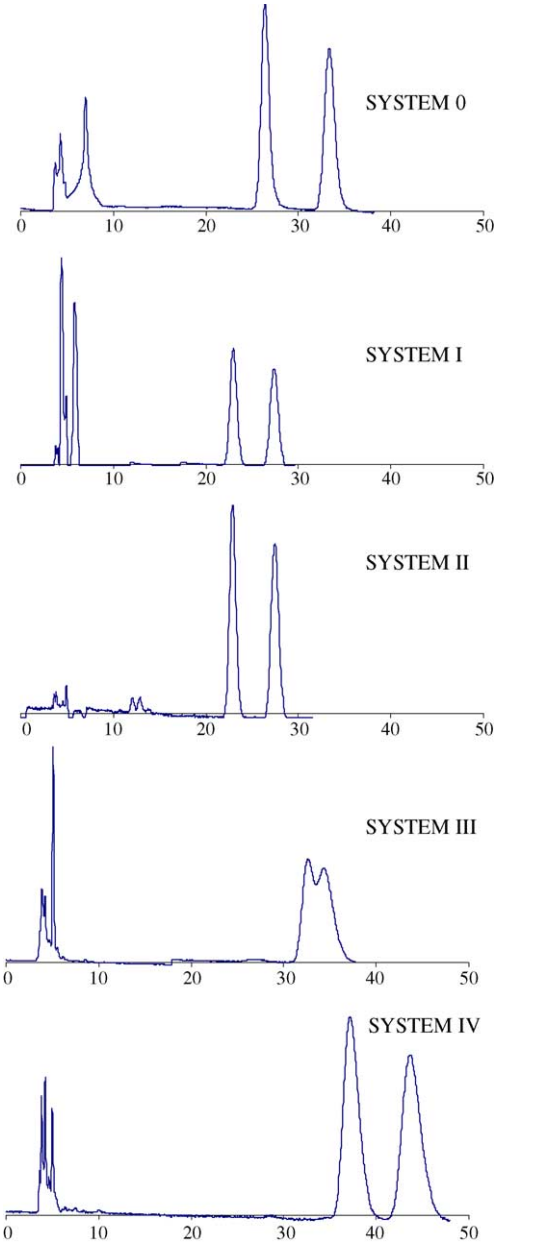


Fig. 4. Chromatograms of sulconazole obtained on Chiracel OD column with various mobile phase composition. Mobile phase hexane:IPA (80:20, v/v)—System 0 and with additives: water (0.2%)—System I, water (0.2%) with AcOH (0.1%)—System II, water (0.2%) with (+) CSA (1.2 mM)—System III and water (0.2%) with (−) CSAs (1.2 mM)—System IV.

3.1.1. System 0, without additives

The retention time of about 30 min was obtained for sulconazole, the retention of miconazole was about 15 min. The retention times for the other studied compounds were very short, near dead volume.

A very nice separation of sulconazole enantiomers was obtained in System 0. For hydroxyzine, doxylamine, miconazole, methoxypheniramine and ephedrine, recognition of the enantiomers can be observed but separation was rather poor. There was no separation for cyclopentolate and homochlorcyclizine.

3.1.2. System I with water

Addition of water did not significantly change the retention time of most of the studied compounds. A small reduction of the retention time was observed for sulconazole and miconazole. The addition of water changed the enantioselectivity of sulconazole from 1.31 to 1.23 but good separation with Rs 2.4 was still obtained. Better separation than in Sys-

tem 0 was obtained for cyclopentolate, hydroxyzine, doxylamine and homochlorcyclizine. The recognition of enantiomers of miconazole, methoxypheniramine and ephedrine was very similar to that of System 0.

3.1.3. System II with acetic acid

For the system with acetic acid, a small increase of retention was observed for cyclopentolate, doxylamine, homochlorcyclizine and methoxypheniramine. The retention of sulconazole and miconazole stayed the same as was the case in System I. The addition of AcOH improved the enantioseparation of hydroxyzine and miconazole. For sulconazole, cyclopentolate and homochlorocyclozine the separation was very similar as in System I. For doxylamine and ephedrine separation was worse than in System I. For methoxypheniramine there was no separation.

3.1.4. Systems III and IV with camphorsulfonic acids

In these systems an increase of retention was observed for all of the studied compounds. Comparing the retention of the studied compounds in the system with (+) and (−) CSAs, it can be seen that for (−) CSA longer retention was obtained for most of the studied compounds, retention was shorter only for hydroxyzine and doxylamine.

After addition of (+) CSA to the mobile phase good separation was obtained only for cyclopentolate. For ephedrine, methoxypheniramine and homochlorocyclozine the enantioseparation was very similar or worse than in System I but the Rs values were higher than in System I. For doxylamine, miconazole and sulconazole, separation was worse than in System I, and for hydroxyzine there was no separation.

For the studied compounds, the best results were obtained in the system with (−) CSA. In this system only the enantiomers of hydroxyzine and homochlorcyclizine were separated very poorly. The rest of the studied compounds displayed very good enantioseparation in this system, with Rs >1.5. However, the separation of sulconazole was better in Systems 0, I and II.

Summing up the results obtained in Systems III and IV, one can see that the data obtained for the Chiralcel OD column modified by (+) and (−) CSA differ significantly. Longer retention and better enantioselectivity was achieved for (−) CSA. The two CSAs as enantiomers can be adsorbed differently at the chiral polysaccharide stationary phase. Therefore, it seems that the interaction between adsorbed acids and basic compounds can act in synergy with or in opposition to the enantioseparation obtained on the polysaccharide phase.

The results show that the enantioselectivity of the two acids could influence the effective enantioselectivity of the system in various ways: (1) both acids may improve the enantioseparation (see results for cyclopentolate), (2) both acids may decrease the enantioseparation; this situation was observed for hydroxyzine, homochlorocyclozine and sulconazole, and (3) for some compounds, one of the CSAs did not change the enantioselectivity and the second CSA improved or decreased the enantioseparation compared to System I with water alone.

It is worth noting that for the very similar enantiselectivity (α) obtained in Systems I and III or IV much better resolution (Rs) was obtained in Systems III and IV than in System I (see results for doxylamine, methoxypheniramine—System IV and ephedrine, cyclopentolate—System III).

3.2. Memory of the column

The memory effect of the mobile phase additives on polysaccharide stationary phase is known [10]. In our experiment we wanted to check what happens after removing the (−) CSA from the mobile phase. After repetitive results were obtained in System IV, the eluent consisting of hexane:IPA 80:20 (v/v) was used. The chromatograms for ephedrine enantiomers obtained on the Chiralcel OD column, with (−) CSA in the mobile phase and after removing the (−) CSA from the mobile phase, are presented in Fig. 5A and B. Additionally the influence of water on the results obtained on dynamically generated new chiral phase was also studied (compare chromatograms in Fig. 5B and C). For the separation of ephedrine enantiomers on the dynamically generated Chiralcel OD by (−) CSA, better results were obtained for eluent with 0.2% water than without water. The results obtained on the dynamically generated new chiral stationary phase were very stable. The retention time, selectivity and resolution controlled during 8 h did not change (compare chromatograms 1 and 2 in Fig. 5B and C).

To obtain information on how the addition of water, AcOH and CSAs influences the performance of the Chiralcel OD column, the chromatographic parameters were checked with the mobile phase as in System 0 after the washing procedure, see results in Table 3.

The addition of water and AcOH did not affect the performance of the column. Unfortunately, the column used with the CSAs, as the additives to the mobile phase did not return to pre-additive behavior even after extensive washing. Not for all but for some of the compounds, especially for ephedrine and homochlorcyclizine, the results obtained after adsorption and desorption of CSAs were not the same as the results obtained on the newly purchased Chiralcel OD column.

To control reproducibility of the separation ability of the Chiralcel OD column after adsorption of (−) CSA the dynamic generation of the column together with the washing procedure was repeated twice. The new chiral stationary phase obtained by adsorption of (−) CSA had very repetitive parameters. In both cases the obtained results were very similar, see Table 2 Systems IVA and B.

3.3. (−) Camphorsulfonic acids on Nucleosil column

To obtain more information about the chiral discrimination properties of the CSAs alone, additional experiments with (−) CSA adsorbed on a Nucleosil column were studied. The comparison of the results obtained for ephedrine enantiomers

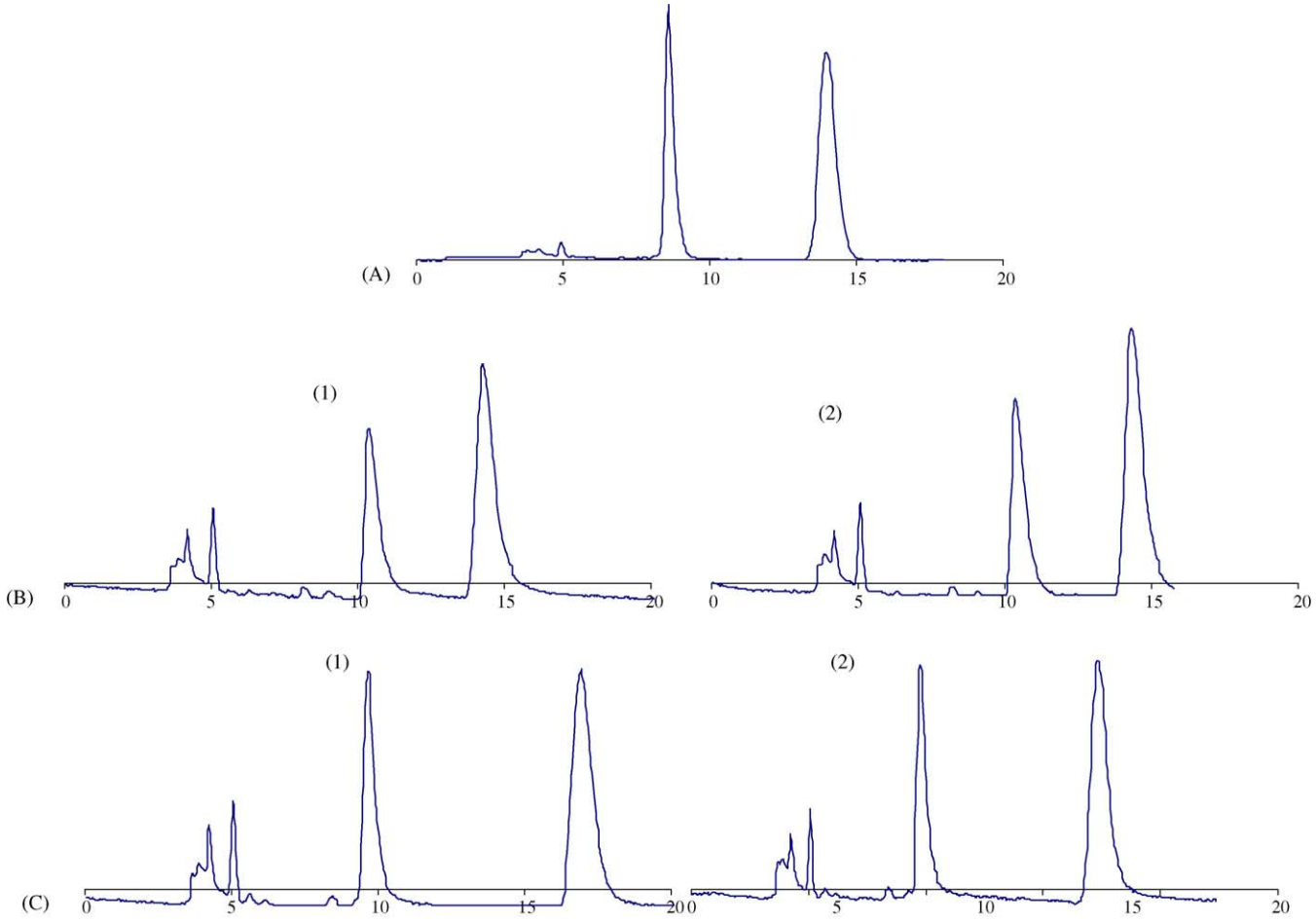


Fig. 5. Comparison of ephedrine enantiomer separation obtained for System IV and after removing (−) CSA from the mobile phase. (A) System IV hexane:IPA (80:20, v/v) with 0.2% water and (−) CSA (1.2 mM). (B) After removing CSA from the mobile phase eluent: hexane:IPA (80:20, v/v). (C) After removing CSA from the mobile phase eluent: hexane:IPA (80:20, v/v) with 0.2% water. (B and C) Experiments after removing (−) CSA from the mobile phase without washing procedure: (1) indicates the first chromatogram obtained after changing the mobile phase and (2) the chromatogram obtained after 8 h.

on the Nucleosil and Chiralcel OD columns is presented in Table 4.

From a separate experiment we know that both the CSA are strongly adsorbed at the Chiralcel OD phase. The strong adsorption of the CSA on hydrophilic stationary phases is also confirmed by the memory of the Chiralcel OD and Nucleosil column (see the results in Table 4 after removing (−) CSA from the mobile phase).

The elution order for ephedrine enantiomers for (−) CSA for the Nucleosil column is opposite to that for the Chiralcel OD column. For the Nucleosil dynamically generated by (−) CSA, the (+) ephedrine was eluted as the first, while for the Chiralcel OD modified by (−) CSA, the (−) ephedrine was eluted as the first. Moreover, the elution order of ephedrine enantiomers on Chiralcel OD was the same for (−) and (+) CSA, which suggests the dominating role of the polysaccha-

Table 3
Parameters of the Chiracel OD described by retention factor, selectivity and resolution obtained after washing procedure (see Section 2) for selected compounds

Compound	20% IPA System 0		20% IPA after System I		20% IPA after System II		20% IPA after System IV	
	k_1 (α)	k_2 (Rs)	k_1 (α)	k_2 (Rs)	k_1 (α)	k_2 (Rs)	k_1 (α)	k_2 (Rs)
Benzoin	1.5 (1.52)	2.3 (5.1)	1.5 (1.52)	2.3 (5.1)	1.5 (1.52)	2.3 (5.1)	1.5 (1.52)	2.3 (5.1)
Sulconazole	6.1 (1.31)	8.0 (3.2)	6.1 (1.31)	8.0 (3.2)	6.1 (1.30)	7.9 (3.2)	6.1 (1.30)	7.9 (3.2)
Hydroxizine	0.8 (1.20)	1.0 (1.1)	0.8 (1.20)	1.0 (1.1)	0.8 (1.20)	1.0 (1.1)	1.0 (1.16)	1.2 (0.8)
Homochlorcyclozine	0.3 (1.00)	0.3	0.3 (1.00)	0.3	0.3 (1.00)	0.3	1.2 (1.7)	2.1 (1.7)
Ephedrine	0.8 (1.32)	1.0 (0.8)	0.8 (1.32)	1.0 (0.8)	0.8 (1.32)	1.0 (0.8)	2.7 (1.11)	3.0 (0.4)

Chromatographic conditions: column Chiracel OD; flow rate 0.8 ml/min, detection 220 nm; mobile phase: hexane:IPA (80:20, v/v).

Table 4
Chromatographic condition for ephedrine enantiomers obtained on Chiracel OD and Nucleosil columns with various mobile phase composition

Mobile phase composition	Nucleosil				Chiracel OD			
	First eluted enantiomer	k_1	α	k_2	First eluted enantiomer	k_1	α	k_2
20% IPA + (−) CSA	(+)	22.5	1.06	23.8	(−)	1.8	1.87	3.3
20% IPA + 0.2% H_2O + (−) CSA	(+)	14.8	1.06	15.5	(−)	1.6	2.18	3.4
20% IPA + 0.2%H_2O[a]	(+)	15.1	1.05	15.8	(−)	1.7	2.25	3.7
20% IPA + 0.2% H_2O + (+) CSA					(−)	1.4	1.24	1.7

[a] After removing (−) CSA from the mobile phase.

ride phase (the elution order is compatible with the elution obtained in System 0).

4. Summary

Small amounts of additives to the mobile phase could be a dynamic part of the system, which changes retention, selectivity, and efficiency of the column. Additives can promote or destroy the chiral recognition of the solute depending on their nature. For the studied compounds an amino nitrogen atom in the structure seems to be very important for changes of the chromatographic parameters with the change of acidic and water additives in the mobile phase. For the reference substance, benzoin, the chromatographic parameters are almost the same in all the studied systems.

The polysaccharide phase is stabilized by numerous Van der Waals contacts and hydrogen bonds [11]. Adsorption of CSAs on polysaccharide can change the conformation of the polysaccharide phase. The changes of enantioseparation ability caused by the adsorption of CSAs on polysaccharide may be due to the changes of the conformation of the stationary phase but interaction between adsorbed acids and the basic compounds cannot be ignored.

Adsorption of (+) and (−) CSA changes the chiral properties of the Chiralcel OD column in different way. For (−) CSA a new stationary phase, with very good enantioseparation ability towards the studied compounds, is obtained.

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