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# Enantioresolution of basic pharmaceuticals using cellulose tris(4-chloro-3-methylphenylcarbamate) as chiral stationary phase and polar organic mobile phases

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ABSTRACT

A polysaccharide-based chiral stationary phase (Sepapak-4), with cellulose tris(4-chloro-3-methylphenylcarbamate) as chiral selector, has been investigated in liquid chromatography (LC). Its enantioresolution power was evaluated towards 13 basic amino-drugs with widely different structures and polarities, using polar organic mobile phases. After preliminary experiments, acetonitrile was selected as the main mobile phase component, to which a low concentration of diethylamine (0.1%) was systematically added in order to obtain efficient and symmetrical peaks. Different organic solvents were first added in small proportions (5–10%) to acetonitrile to modulate analyte retention. Polar organic modifiers were found to decrease retention and enantioresolution while hexane had the opposite effect, indicating normal-phase behaviour under these conditions. The addition of an organic acid (formic, acetic or trifluoroacetic acid) was found to strongly influence the retention of the basic amino drugs in these nonaqueous systems. The nature and proportion of the acidic additive in the mobile phase had also deep impact on enantioresolution. Therefore, the studied compounds could be subdivided in three groups in respect to the acidic additive used. All analytes could be enantioseparated in relatively short analysis times (10–20 min) using these LC conditions.



## 1. Introduction

Over the last decade, many efforts have been focused on the development of original chiral stationary phases (CSPs), either by immobilizing the chiral selector on silica support to extend the choice of modifiers or additives in the mobile phase or by proposing new chiral selectors.

Polysaccharide derivatives are the most commonly used CSPs for direct liquid chromatographic (LC) enantioseparation of chiral compounds. In particular, the phases composed of cellulose phenylcarbamate or amylose derivatives as chiral selectors have shown a wide range of applications [1–4]. Their enantioresolution ability often depends on the structure of the chiral polymers but also on the substituents of the phenyl group in the case of phenylcarbamate derivatives [5]. Okamoto and co-workers reported that the derivatives having an electron-donating substituent, such as a methyl group in the 3- or 4-positions of the phenyl moeity, show a high chiral recognition due to the higher order structure of the chiral selector adsorbed on silica. Moreover, 3,5-disubstituted phenylcarbamates of cellulose (either by methyl groups or by chloro groups) also show a high enantioresolution power [3]. Nevertheless, the high solubility of the dichlorophenylcarbamate derivative in organic solvents can be problematic. In order to enhance the chiral recognition, Chankvetadze et al. have developed new polysaccharidic CSPs substituted by methyl and chloro groups in positions 3 and 4 of the phenyl moiety [6–9].

Initially the normal-phase liquid chromatography (NPLC) was proposed for all these CSPs. However, it was shown later that not only reversed-phase LC (RPLC) with aqueous–organic mobile phases [10–18], but also polar organic solvent chromatography (POSC) can be applied [19,20].

Since the development of polysaccharides-based CSPs by Okamoto and co-workers [3,5,21–23] and the commercialization of derivatives, only a few efforts have been focused on the study of the effects of factors, such as the acidic additives, which can play a crucial role in polar organic solvent chromatography with respect to chiral selectivity. To the best of our knowledge, although some previous studies have shown the role of basic and acidic additives

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for enantioseparation in NPLC [24–26], only few systematic comparative studies have been reported in POSC concerning the use of polysaccharides-based CSPs with different acidic additives for separation of enantiomers [20,27].

In the present study, the chiral recognition ability of a polysaccharide-based CSP with cellulose tris(4-chloro-3-methylphenylcarbamate) as chiral selector (cf. Fig. 1A), namely Sepapak-4, was evaluated for the enantioseparation of 13 basic amino-drugs with widely different structures and polarities (cf. Fig. 1B). Acetonitrile was used as main solvent with basic and acidic additives in POSC. The effect of factors likely to influence the chromatographic parameters such as retention, selectivity and enantioresolution on Sepapak-4, was examined.

## 2. Experimental

### 2.1. Chemicals and reagents

Acebutolol hydrochloride, metoprolol tartrate, oxprenolol hydrochloride, propranolol hydrochloride, econazole nitrate and prilocaine hydrochloride were supplied by Sigma–Aldrich (Saint-Louis, MO, USA). Celiprolol hydrochloride was provided by Rorer (Brussels, Belgium), miconazole nitrate by Janssen Pharmaceutica (Beerse, Belgium), sotalol hydrochloride by Profarmaco Combrex (Milan, Italy), atenolol by Erregierre (Bergamo, Italy), betaxolol by LERS (Paris, France), bupivacaine hydrochloride by Astra Pharmaceutical Products (Södertalje, Sweden) and mepivacaine hydrochloride by Federa (Brussels, Belgium). All samples are racemates used without further purification.

Acetonitrile (ACN), methanol, ethanol and 2-propanol of HPLC grade and glacial acetic acid (AcA) pro analysi were provided by Merck (Darmstadt, Germany). Trifluoroacetic acid (TFA), diethylamine (DEA) and formic acid (FA) pro analysi were obtained from Acros Organics (Geel, Belgium) and *n*-hexane from BDH Hypersol (Poole, UK).

### 2.2. Instrumentation

The chromatographic system from Agilent Technologies (Waldbronn, Germany) consisted in a binary pump, a thermostated column compartment, a diode array detector and an automatic injector, all of 1100 series. The Chemstation software was used for system control and data acquisition. The chiral column Sepapak-4 (250 mm × 4.6 mm I.D.) was kindly provided by Sepaserve (Münster, Germany).

The chiral selector adsorbed on aminopropylsilanized silica (nominal particle size 5 μm and nominal pore diameter 100 nm) was cellulose tris(4-chloro-3-methylphenylcarbamate) in the amount of 25% (w/w).

### 2.3. Solutions for method development

The mobile phases used of the different experiments were prepared by mixing the required proportions of acetonitrile, organic modifier (methanol or hexane) and acidic additives (TFA; FA; AcA). Then 0.1% of DEA (9.7 mM) was systematically added. Analytical solutions of racemate compounds of nearly 100 μg/ml were prepared by dissolving the appropriate amount of the substance in the required volume of mobile phase.

### 2.4. Chromatographic conditions

The mobile phases consisted in a mixture of acetonitrile, organic modifier (methanol or hexane), acidic additive and DEA (v/v) and were pumped at a constant flow-rate of 1.0 mL $min^{-1}$. In the different experiments, the DEA percentage in the mobile phase was settled at 0.1%. The injection volume was 20 μL. The analytes were detected photometrically at 220 nm.

## 3. Results and discussion

Originally dedicated for normal- and reversed-phases, polysaccharidic CSPs provided good results in POSC [19,28–32]. In this system, only polar organic solvents such as acetonitrile, methanol, 2-propanol and their mixtures are used. Methanol and acetonitrile were tested as the main component of the mobile phase and the best results were obtained with acetonitrile. These results confirm observations made by others [29]. Therefore, acetonitrile was selected as the main solvent.

In addition to the classical factors such as temperature, pH and type of organic modifier, which can influence the enantioseparation in LC, several authors demonstrated that the acidic and basic mobile phase additives can also have a significant impact [20,24,33,34]. In these studies mostly carried out in normal-phase, these additives were supposed to minimize the non-specific interactions between the analytes and the free silanol groups of the CSP. Nevertheless, these additives are known to have a strong affinity for the CSP [20,24,33,34]. Therefore, the present study protocol includes a rinsing procedure with neat acetonitrile for 1 h followed by an equilibration of the CSP with the mobile phase containing both acidic and basic additives for 1 h.

Since few information on the behaviour of Sepapak-4 in POSC is available, this screening study was conducted following a classical method development. In accordance with the literature, the studied factors are those commonly investigated, namely the temperature, the nature and the proportion of the organic modifier as well as the acidic additive. It has been checked that the nature of the basic additive, namely diethyamine, triethylamine and butylamine, had no significant influence on enantioresolution, as already observed in the literature for polysaccharide based CSP [20].

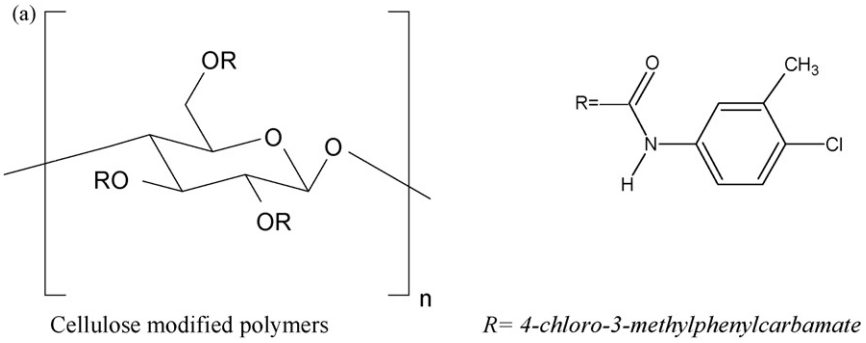
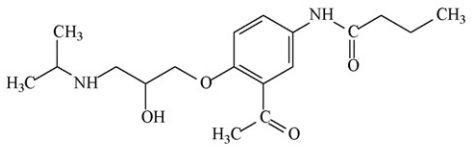
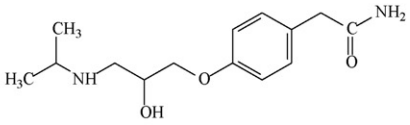



**Fig. 1.** Structure of Sepapak-4 chiral selector (A) and molecular structures of the studied basic amino drugs (B).

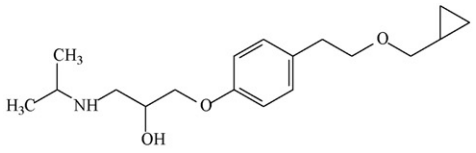
(b)



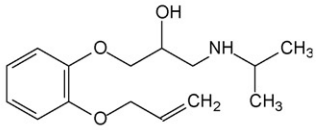
Acebutolol



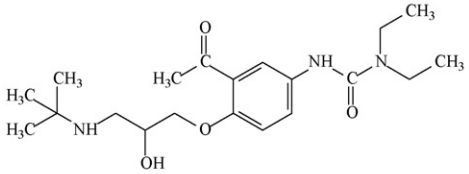
Atenolol



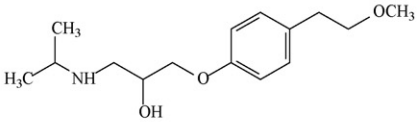
Betaxolol



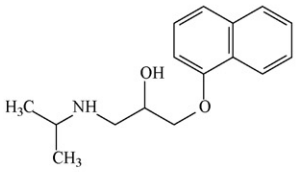
Oxprenolol



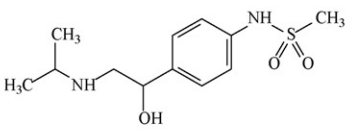
Celiprolol



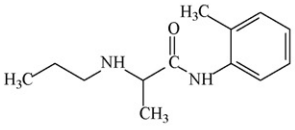
Metoprolol



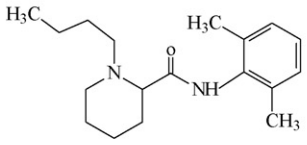
Propranolol



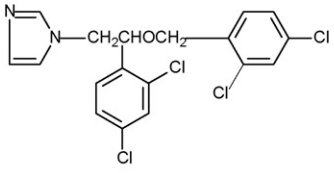
Sotalol



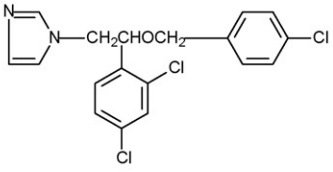
Prilocaïne



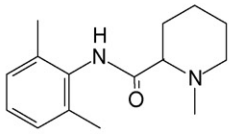
Bupivacaine



Miconazole



Econazole



Mepivacaine

**Fig. 1.** ( *Continued* ).

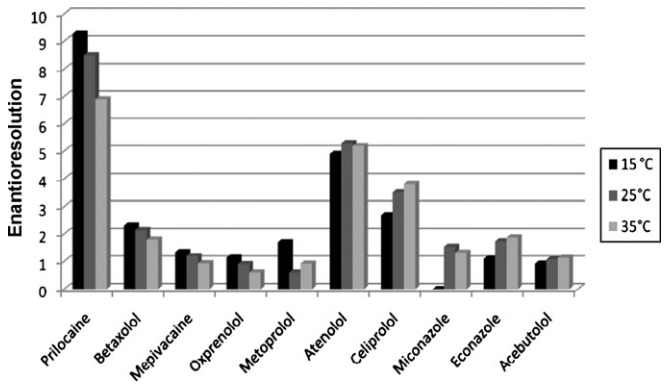



**Fig. 2.** Influence of the temperature on enantioresolution. Mobile phase: ACN/0.1% DEA/0.1% TFA; temperature: 15, 25 and 35 °C. Other conditions: see Section 2.

### 3.1. Effect of the temperature

The influence of the temperature on the enantioresolution ($R_s$) of the studied chiral drugs was investigated (cf. Fig. 2). As can be seen in this figure, the change in enantioresolution with temperature seems to be generally rather limited and very much compound dependent. For those which exhibited an increased enantioresolution with temperature, a significant efficiency enhancement was observed at 35 °C (e.g. for celiprolol, plate number ($N$) increases from 3200 at 15 °C to 6500 at 35 °C). The latter effect seems to be mainly responsible for the observed improvement in resolution. However, for three compounds with low enantioresolution (namely, mepivacaine, oxprenolol and metoprolol, cf. Fig. 2) high temperature is defavourable. Finally, it was decided to select 15 °C for further investigations.

### 3.2. Effect of the addition of an organic modifier

As illustrated in Fig. 3 for atenolol enantiomers, the addition of 10% hexane in the mobile phase increased the retention and the enantioresolution of most of the studied molecules, unlike methanol, confirming the involvement of hydrogen-bond interactions between the analyte and the chiral selector. Therefore, these results clearly show that a polar organic modifier increases the elution capacity of the mobile phase, in accordance with Lyman and Stringham's work [32], indicating a normal-phase behaviour where

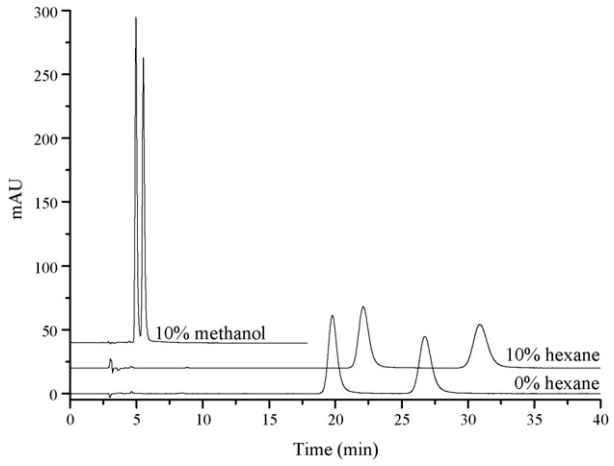



**Fig. 3.** Chromatograms illustrating the effect of $n$-hexane or methanol addition in the mobile phase on atenolol enantiomers resolution. Mobile phase: ACN/0.1% DEA/0.1% TFA/$x$ (0% or 10%) hexane or methanol; temperature: 15 °C. Other conditions: see Section 2.

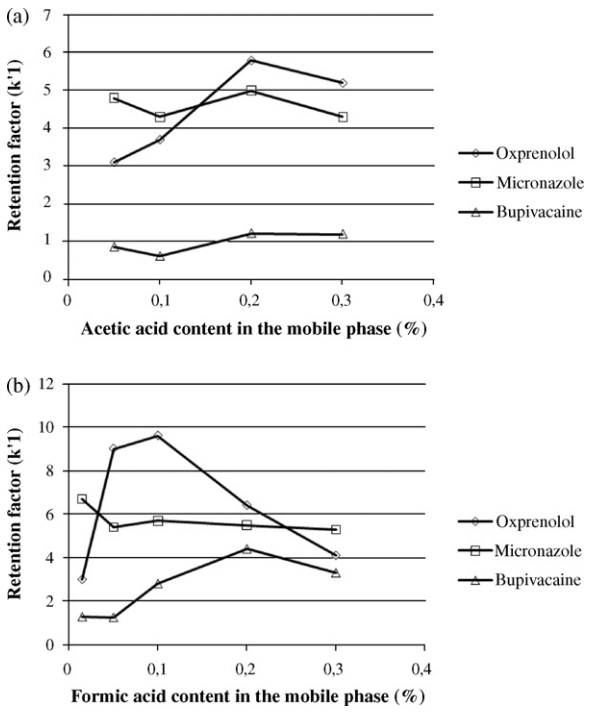



**Fig. 4.** Influence of the acetic (A) and formic (B) acid proportion in the mobile phase on the retention factor ($k'_1$). Mobile phase: ACN/0.1% DEA/(0.05–0.3%) AcA (A) or ACN/0.1% DEA/(0.015–0.3%) FA (B); temperature: 15 °C. Other conditions: see Section 2.

the hydrogen-bond interactions are regulated by the nature and the proportion of the organic modifier.

### 3.3. Effect of the nature of the acidic additive

The importance of the nature of the acidic additive was also demonstrated. Table 1 presents the retention factor, the enantioresolution and selectivity values obtained in the presence of 0.1% TFA (13.5 mM), acetic acid (26.5 mM) and formic acid (17.5 mM). As can be seen in this table, the enantiomers of propranolol, sotalol, miconazole and bupivacaine were not resolved when TFA was used as an acidic modifier, while a complete enantioseparation was observed in the presence of formic acid and/or acetic acid. The best enantioresolution of the β-blockers (except for oxprenolol, propranolol and sotalol) and prilocaine was obtained with TFA while the best results for the imidazole derivatives (econazole and miconazole) and sotalol were observed with acetic acid. As for the other local anaesthetics (bupivacaine and mepivacaine), oxprenolol and propranolol, formic acid gave rise to the highest $R_s$ values. Moreover, this acid led to the strongest retention for all studied compounds, which indicates that the acidic character of the additive is not the only factor decreasing retention. Indeed, formic acid is stronger than acetic acid but gives rise to higher retention. Obviously, other factors intervene in the interactions between the analytes and the CSP such as possibly ion-pair formation which is in principle stronger for acetic acid than formic acid. Results from Table 1 clearly show that acidic additives have also an important effect on enantioresolution and selectivity by contrast to data obtained with classical cellulose or amylose tris(3,5-dimethylphenylcarbamate) based CSP [33]. Therefore, it can be assumed that the introduction of chlorine on the phenyl moiety of Sepapak-4 has a deep impact on the ability of acidic additives to enhance enantioresolution. This might be explained by a reduction of non-specific interactions with the CSP due to the presence of acidic additive in the mobile phase [24,33,34].

**Table 1**
Influence of the acidic additive nature in the mobile phase on the retention factor ($k'_1$), the enantioresolution ($R_s$) and selectivity ($\alpha$) of the studied basic amino-drugs using Sepapak-4.

| | 0.1% TFA | | | 0.1% AcA | | | 0.1% FA | | |
|---|---|---|---|---|---|---|---|---|---|
| | $k'_1$ | $R_s$ | $\alpha$ | $k'_1$ | $R_s$ | $\alpha$ | $k'_1$ | $R_s$ | $\alpha$ |
| Acebutolol | 1.50 | **0.92** | 1.09 | / | / | / | / | / | / |
| Atenolol | 5.1 | **4.9** | 1.42 | / | / | / | / | / | / |
| Betaxolol | 0.55 | **2.3** | 1.34 | 5.4 | 1.13 | 1.09 | 13.8 | – | – |
| Celiprolol | 2.2 | **2.7** | 1.31 | / | / | / | / | / | / |
| Metoprolol | 0.48 | **1.71** | 1.26 | 5.0 | 0.77 | 1.06 | 12.4 | – | – |
| Oxprenolol | 0.38 | 1.14 | 1.20 | 3.7 | **2.2** | 1.17 | 9.6 | **2.3** | 1.16 |
| Propranolol | 0.28 | – | – | 4.6 | 1.20 | 1.08 | 12.3 | **2.2** | 1.15 |
| Sotalol | 0.16 | – | – | 4.1 | **1.85** | 1.16 | 12.0 | 1.50 | 1.11 |
| Econazole | 1.31 | 1.10 | 1.10 | 3.0 | **6.4** | 1.55 | 4.1 | **6.1** | 1.48 |
| Miconazole | 1.90 | – | – | 4.3 | **3.9** | 1.29 | 5.7 | 2.7 | 1.19 |
| Bupivacaine | 0.72 | – | – | 0.62 | – | – | 2.8 | **2.6** | 1.19 |
| Mepivacaine | 0.64 | 1.35 | 1.16 | 0.65 | 1.21 | 1.19 | 2.6 | **2.5** | 1.19 |
| Prilocaine | 0.55 | **9.3** | 2.7 | 0.29 | 1.82 | 1.36 | 1.85 | 1.22 | 1.09 |

'/' no peak obtained within 60 min. '–' no enantioresolution observed. Mobile phase: ACN/0.1% DEA/0.1% (TFA: 13.5 mM, AcA: 26.5 mM or FA: 17.5 mM); temperature: 15 °C; other conditions: see Section 2. Bold values: highest $R_s$ values obtained for each analyte.

**Table 2**
Influence of acetic acid proportion in the mobile phase on the enantioresolution ($R_s$) and selectivity ($\alpha$) of the studied basic amino-drugs using Sepapak-4.

| | Acetic acid (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0.05[a] | | 0.1[b] | | 0.2[c] | | 0.3[d] | |
| | $R_s$ | $\alpha$ | $R_s$ | $\alpha$ | $R_s$ | $\alpha$ | $R_s$ | $\alpha$ |
| Acebutolol | / | / | / | / | / | / | / | / |
| Atenolol | / | / | / | / | / | / | / | / |
| Betaxolol | 1.56 | 1.11 | 1.31 | 1.09 | 1.46 | 1.10 | 0.89 | 1.06 |
| Celiprolol | / | / | / | / | / | / | / | / |
| Metoprolol | 1.08 | 1.07 | 0.80 | 1.06 | 0.80 | 1.06 | – | – |
| Oxprenolol | 2.3 | 1.17 | 2.2 | 1.17 | 2.4 | 1.17 | 1.98 | 1.42 |
| Propranolol | 0.95 | 1.07 | 1.20 | 1.11 | 1.54 | 1.11 | 2.1 | 1.15 |
| Sotalol | 1.93 | 1.17 | 1.85 | 1.15 | 1.89 | 1.15 | 1.50 | 1.13 |
| Econazole | 6.7 | 1.53 | 6.4 | 1.51 | 6.1 | 1.51 | 5.8 | 1.50 |
| Miconazole | 3.9 | 1.30 | 3.9 | 1.26 | 3.6 | 1.26 | 3.4 | 1.25 |
| Bupivacaine | – | – | – | – | – | – | – | – |
| Mepivacaine | 1.35 | 1.14 | 1.21 | 1.11 | 1.20 | 1.11 | 1.20 | 1.12 |
| Prilocaine | 2.2 | 1.35 | 1.82 | 1.14 | 1.38 | 1.14 | – | – |

'/' no peak obtained within 60 min. '–' no enantioresolution observed. Mobile phase: ACN/0.1% DEA/(0.05–0.3)% AcA; temperature: 15 °C; other conditions: see Section 2. 'a,b,c,d' letters refer to molar concentrations of acidic additives: (a) 8.7 mM; (b) 17.5 mM; (c) 35 mM; (d) 52.5 mM.

### 3.4. Effect of the proportion of the acidic additive

Fig. 4 illustrates the influence of the proportion of acetic and formic acids on the retention factor. Since all compounds of the same class exhibited similar behavior, only the results obtained for one compound of each class is presented in Fig. 4. It is worth noting that the percentage of TFA was not investigated since proportions lower or higher than 0.1% led to a very unstable baseline and to a very low retention. As can be seen in Fig. 4, similar effects were observed for the two acidic additives but the influence of acetic acid concentration seems to be less pronounced. A tendency to an increase in retention with the acidic additive con-

**Table 3**
Influence of formic acid proportion in the mobile phase on the enantioresolution ($R_s$) and selectivity ($\alpha$) of the studied basic amino-drugs using Sepapak-4.

| | Formic acid (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0.015[a] | | 0.05[b] | | 0.1[c] | | 0.2[d] | | 0.3[e] | |
| | $R_s$ | $\alpha$ | $R_s$ | $\alpha$ | $R_s$ | $\alpha$ | $R_s$ | $\alpha$ | $R_s$ | $\alpha$ |
| Acebutolol | – | – | / | / | / | / | / | / | 1.32 | 1.09 |
| Atenolol | / | / | / | / | / | / | / | / | / | / |
| Betaxolol | – | – | – | – | – | – | 0.6 | 1.05 | / | / |
| Celiprolol | / | / | / | / | / | / | / | / | – | – |
| Metoprolol | – | – | – | – | – | – | – | 1 | – | – |
| Oxprenolol | 1.53 | 1.12 | 1.68 | 1.11 | 2.3 | 1.16 | 2.4 | 1.16 | 2.4 | 1.15 |
| Propranolol | 1.62 | 1.12 | 1.82 | 1.12 | 2.2 | 1.15 | 2.3 | 1.16 | 2.3 | 1.16 |
| Sotalol | 0.77 | 1.07 | 1.01 | 1.07 | 1.50 | 1.11 | 1.60 | 1.12 | 1.57 | 1.10 |
| Econazole | 7.7 | 1.59 | 7.0 | 1.58 | 6.1 | 1.48 | 3.7 | 1.28 | 2.6 | 1.16 |
| Miconazole | 3.9 | 1.24 | 3.2 | 1.23 | 2.7 | 1.19 | 1.39 | 1.09 | – | – |
| Bupivacaine | – | – | – | – | 2.6 | 1.19 | 3.2 | 1.22 | 2.9 | 1.18 |
| Mepivacaine | 1.49 | 1.14 | 1.28 | 1.14 | 2.5 | 1.19 | 2.9 | 1.21 | 3.3 | 1.27 |
| Prilocaine | 2.9 | 1.34 | 1.75 | 1.21 | 1.22 | 1.09 | 1.09 | 1.21 | 2.7 | 1.27 |

'/' no peak obtained after 60 min. '–' no enantioresolution observed. Mobile phase: ACN/0.1% DEA/(0.015–0.3)% FA; temperature: 15 °C; other conditions: see Section 2. 'a,b,c,d,e' letters refer to molar concentration of acidic additives: (a) 4 mM; (b) 13.2 mM; (c) 26.5 mM; (d) 53 mM; (e) 79.5 mM.

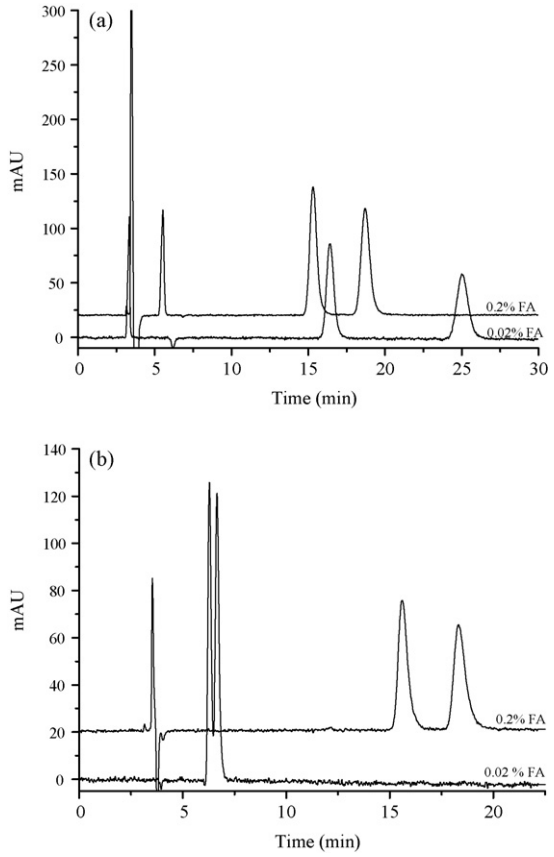



**Fig. 5.** Chromatograms of econazole (A) and mepivacaine (B) enantiomers illustrating the effect of formic acid proportion on enantioresolution. Mobile phase: ACN/0.1% DEA/ (0.02–0.2%) FA; temperature: 15 °C. Other conditions: see Section 2.

tent was found for most compounds and seems to be related to their basic character, since only the two analytes with low p$K_a$ values, namely the two imidazole derivatives, showed an opposite trend.

Tables 2 and 3 present the effect of acetic and formic acids proportion in the mobile phase on the enantioresolution and selectivity values of the studied basic drugs. As can be seen in these tables, the influence of the acidic additive concentration on enantioresolution and selectivity seems to follow the same trend as observed for retention (cf. Fig. 4). In most cases, $R_s$ and selectivity values were found to increase with acidic additive percentage, except for acetic acid which shows an opposite effect (cf. Tables 1–3). By contrast, a significant decrease in enantioresolution and selectivity was obtained for the two less basic compounds (i.e. the imidazole derivatives).

The chromatograms illustrated in Fig. 5 show that an increase of the formic acid concentration in the mobile phase gives rise to a decrease of the econazole retention and enantioresolution whereas the opposite trend is observed for the more basic mepivacaine. It is worth noting that higher concentrations (>0.2%) are not recommended because they have a tendency to give rise to noisy baseline.

Therefore, two groups of substances could be distinguished from Tables 1–3, according to the acidic additive used. The first group is constituted of atenolol, celiprolol, acebutolol, betaxolol, metoprolol and prilocaine. For these compounds, TFA gives rise to the best enantioresolution. The second group includes the other compounds, i.e. bupivacaine, mepivacaine, econazole, miconazole oxprenolol, propranolol and sotalol for which a high enantiomeric separation is observed with formic acid

## 4. Conclusion

The newly commercialized chiral stationary phase Sepapak-4 was tested with acetonitrile as main mobile phase component and 0.1% of basic additive (DEA). The results showed a significant effect of acidic additive nature and concentration on retention, selectivity and enantioresolution of the basic chiral compounds. The studied CSP demonstrated good chiral discrimination ability. Temperature, the type and concentration of the acidic additive as well as the presence of an organic modifier in the mobile phase were found to be important parameters to optimize retention and enantioresolution. Furthermore, the tested compounds showed different behaviours and can be classified in two groups according to the acidic additive selected. These results will be exploited to perform multivariate screening and optimization of enantioresolution on this CSP.

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