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Comparison of chiral recognition capabilities of cyclodextrins for the separation of basic drugs in capillary zone electrophoresis

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Abstract

The enantiomeric separation of some racemic anti-histamines and anti-malarials, namely (±)-pheniramine, (±)-brompheniramine, (±)-chlorpheniramine, (±)-doxylamine, and (±)-chloroquine, was investigated by capillary zone electrophoresis. The enantiomeric separation of five compounds was obtained by addition of ~7 m*M* (1%, w/v) sulfated-β-cyclodextrin into the buffer as a chiral selector. The effects of sulfated-β-cyclodextrin concentration and buffer pH on migration and resolution are discussed. Two other cyclodextrins, carboxyethylated-β-cyclodextrin and hydroxypropyl-β-cyclodextrin were also investigated. Four of the racemic compounds were resolved using 14 m*M* (2%, w/v) carboxyethylated-β-cyclodextrin while 28 m*M* (4%, w/v) hydroxypropyl-β-cyclodextrin resolved only two of them. It was found that the type of substituent and the degree of substitution on the rim of the CD structure played an important role in enhancing the chiral recognition. Cyclodextrins with negatively charged substituents and higher degree of substitution on the rim of the structure proved to give better resolution to the cationic racemic compounds compared with cyclodextrin with neutral substituents. This is due to the countercurrent mobility of the negatively charged cyclodextrin relative to the cationic analytes thus allowing for a smaller difference in interaction constants to achieve a successful resolution of enantiomers. Furthermore, lower concentrations of negatively charged cyclodextrins were necessary to achieve the equivalent resolutions as compared with the neutral ones.

Keywords: Enantiomer separation; Cyclodextrins; Pheniramine; Brompheniramine; Chlorpheniramine; Doxylamine; Chloroquine

1. Introduction

The analytical resolution of enantiomers is an important subject, especially in the pharmaceutical industry and medical field due to the different physiological activity of each antipode. Chiral gas chromatography (GC) and liquid chromatography (LC) were the first tools employed to perform chiral separation [1–3].

Capillary electrophoresis (CE) is becoming a powerful and popular analytical technique due to its rapid analysis, high resolution and low cost. Several different separation modes, namely capillary gel electrophoresis (CGE), micellar electrokinetic chromatography (MEKC), capillary isotachophoresis (CITP) and capillary zone electrophoresis (CZE)

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have been widely used [4,5]. The ready availability of many chiral selectors has made CE successful for chiral analysis in the pharmaceutical industry [3]. Chiral selectors which have been successfully used in CE for chiral separation include cyclodextrins (CDs) and their derivatives, modified crown ether derivatives, proteins, antibiotics, linear saccharides, chiral surfactants and chiral polymers [6,7]. Among different chiral selectors, four separation principles are proposed, i.e., (1) inclusion–complexation using CDs and their derivatives, antibiotics and crown ether derivatives; (2) chiral ligand-exchange complexation using proteins; (3) chiral micellar solubilization with chiral surfactants; and (4) chiral polymer-based recognition with chiral polymers [6,7].

Among the commercially available CDs are the uncharged native CDs, i.e., α-, β- and γ-CD, the uncharged derivatized CDs, mainly hydroxypropyl-β-CD (HP-β-CD), heptakis (2,6-di-*O*-methyl)-β-CD (di-OMe-β-CD) and heptakis (2,3,6-tri-*O*-methyl)-β-CD (tri-OMe-β-CD), and modified charged CDs, such as carboxymethylated-β-CD (CM-β-CD), carboxyethylated-β-CD (CE-β-CD), sulfobutyl ether β-CD(IV) [β-CD-SBE(IV)] and sulfated-β-CD. The native and modified CDs have been successfully employed for enantiomeric separations [6].

Differently substituted CDs have been investigated and compared recently by some groups for their chiral recognition capabilities. The chiral recognition power of sulfated-β-CD for charged and neutral analytes has been demonstrated by Stalcup and Gahm [8]. Reversed voltage and low pH were adopted in their experiment. Neutral or cationic analytes were brought to and detected at the anode only when they interacted with sulfated-β-CD. Another widely studied anionic CD is sulfobutyl ether β-CD(IV) which is the sodium salt of a randomly substituted sulfobutyl ether β-CD with an average degree of alkylation of approximately 4 [9]. Tait et al. [9] demonstrated that the chiral discrimination of (±)-ephedrine was achieved with only 1.5 m*M* β-CD-SBE(IV) while 20 m*M* di-OMe-β-CD had been used for the same analyte. Schmitt and Engelhardt [10] reported the use of reversed voltage with coated capillary for the separation of neutral and cationic analytes at pH 5.8 using CE-β-CD and CM-β-CD as chiral selectors. CE-β-CD resolved hexobarbital and binaphthol better than CM-β-CD. As demonstrated by Aumatell et al. [11], HP-β-CD (degree of substitution, DS 0.8) proved to be a better chiral selector than HP-β-CD DS 0.6 for the separation of clenbuterol and terbutaline. Fanali and Aturk [12] demonstrated that tri-OMe-β-CD gave better resolution than di-OMe-β-CD for the separation of six anti-inflammatory drugs. Weseloh et al. [13] also reported that good separations occurred with tri-OMe-β-CD with short migration times of the enantiomers of six basic drugs (tranylcypromine etc.). Nishi et al. [14] reported that di-OMe-β-CD resolved 14 drugs, including trimetoquinol etc., and was the most effective for the chiral recognition of the enantiomers studied among four CDs employed, i.e., di-OMe-β-CD, tri-OMe-β-CD, β-CD and γ-CD.

Antihistamines and antimalarials discussed in this work are known to be administered as racemic mixtures. Separation of these drugs has been performed by Stalcup and Gahm [8] using sulfated-β-CD as a chiral selector. Only (±)-brompheniramine, (±)-chlorpheniramine and (±)-chloroquine were well resolved. Separation of (±)-chlorpheniramine by β-CD, HP-β-CD, di-OMe-β-CD and tri-OMe-β-CD has also been reported [15–18]. (±)-Doxylamine was separated using CM-β-CD as buffer additive [10].

In this work, modified CDs, i.e., sulfated-β-CD, CE-β-CD and HP-β-CD were employed to separate five basic drugs. The effect of the structure of CDs on the chiral recognition capabilities in the CZE mode was investigated.

2. Experimental

Sulfated-β-CD and HP-β-CD were purchased from Aldrich Chemical (Milwaukee, WI, USA). CE-β-CD was from Cyclolab (Budapest, Hungary). (±)-Pheniramine, (±)-chlorpheniramine, (±)- brompheniramine, (±)-doxylamine, and (±)-chloroquine were purchased from Sigma (St. Louis, MO, USA). Sodium dihydrogenphosphate dihydrate and disodium hydrogenphosphate anhydrous were from Fluka (Buchs, Switzerland).

Buffers were prepared with water purified with a Millipore-Q system (Millipore, Bedford, MA, USA). The buffer electrolyte was 10 m*M*, 20 m*M* and 50 m*M* phosphate, prepared by mixing equimolar solu-

tions of NaH_2PO_4 and Na_2HPO_4 or adjusted with phosphoric acid to the desired pH. Stock standard solutions of each drug were prepared in 10 m*M* phosphate buffer and diluted to approximately 100 ppm with 10 m*M* phosphate at pH 3.84.

Two commercial formulations, namely chlorpheniramine maleate and chloroquine phosphate containing chlorpheniramine (4 mg per tablet) and chloroquine (250 mg per tablet) were prepared by dissolving each tablet with water in 10-ml and 25-ml volumetric flasks, respectively. After sonication for 5 min, the samples were filtered through 0.45-μm filters and diluted to obtain two stock solutions containing about 0.4 mg/ml and 1 mg/ml of chlorpheniramine and chloroquine. The stock solutions were further diluted with water to approximately 100 ppm and injected for electrophoretic analysis.

CZE was performed on a laboratory-built system. Fused-silica capillaries of 34/57 cm effective/total length×75 μm I.D. (Polymicro Technologies, Phoenix, AZ, USA) were used as separation columns. New capillaries were pretreated by rinsing with 0.1 *M* NaOH for 10 min, with water for 5 min and with buffer for 5 min before injection. The capillary was rinsed before each run with 0.1 *M* NaOH (5 min), water (5 min) and buffer (5 min). When CE-β-CD was added into the buffer as a chiral selector, the capillary was rinsed with water (5 min) and buffer (5 min) before each run. In this case, no NaOH was used to flush the capillary. Injection was performed hydrodynamically at a height difference of 14 cm. A PS-2 power supply (CE Resources, Singapore) was employed. On-column detection was carried out at 214 nm with a Perkin-Elmer Bio UV–Vis Spectrophotometric detector (Model LC290, Foster City, CA, USA). Data processing was performed on a Hewlett-Packard integrator (Model HP3394A, Avondale, PA, USA).

3. Results and discussion

Sulfated-β-CD, CE-β-CD and HP-β-CD were used to separate five basic drugs. All the drugs studied were resolved by sulfated-β-CD. CE-β-CD achieved chiral recognition of four of them while HP-β-CD only two. The chiral recognition capabilities and the structures of CDs were examined.

3.1. Sulfated-β-CD as a chiral selector

The enantiomeric separation of five anti-histamines and anti-malarials was studied in the absence and presence of sulfated-β-CD in the pH range 2.8–5.8, respectively. The structures of these compounds are shown in Fig. 1. In the absence of sulfated-β-CD all analytes were positively charged and migrated towards the cathode with migration rates faster than the electroosmotic flow (EOF). No resolution of enantiomers was observed due to the fact that enantiomers of the same compound possessed the same physicochemical properties in achiral conditions [19]. However, in the presence of sulfated-β-CD which was negatively charged at all conditions, analytes interacted with sulfated-β-CD and formed diastereoisomers which had different properties giving rise to differences in selectivity. The migration of the analytes towards the cathode was retarded thus allowing for chiral recognition of the analytes.

3.1.1. Effects of sulfated-β-CD concentration on migration and resolution

The effects of sulfated-β-CD concentration on the resolution were investigated at pH 3.84. The results are shown in Fig. 2. The migration times and resolution of (±)-pheniramine, (±)-chlorpheniramine

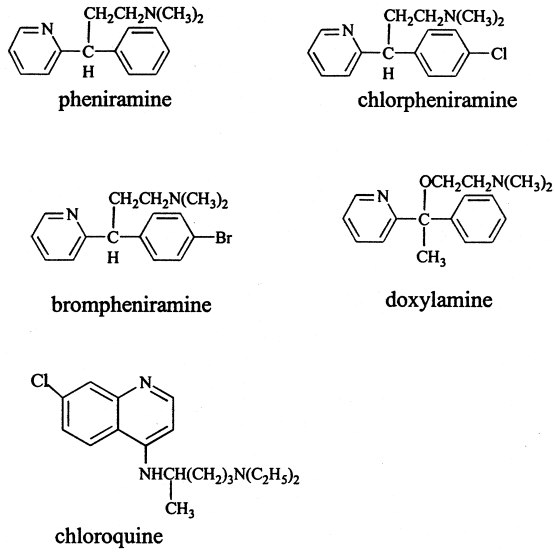

Fig. 1. Structures of compounds studied.

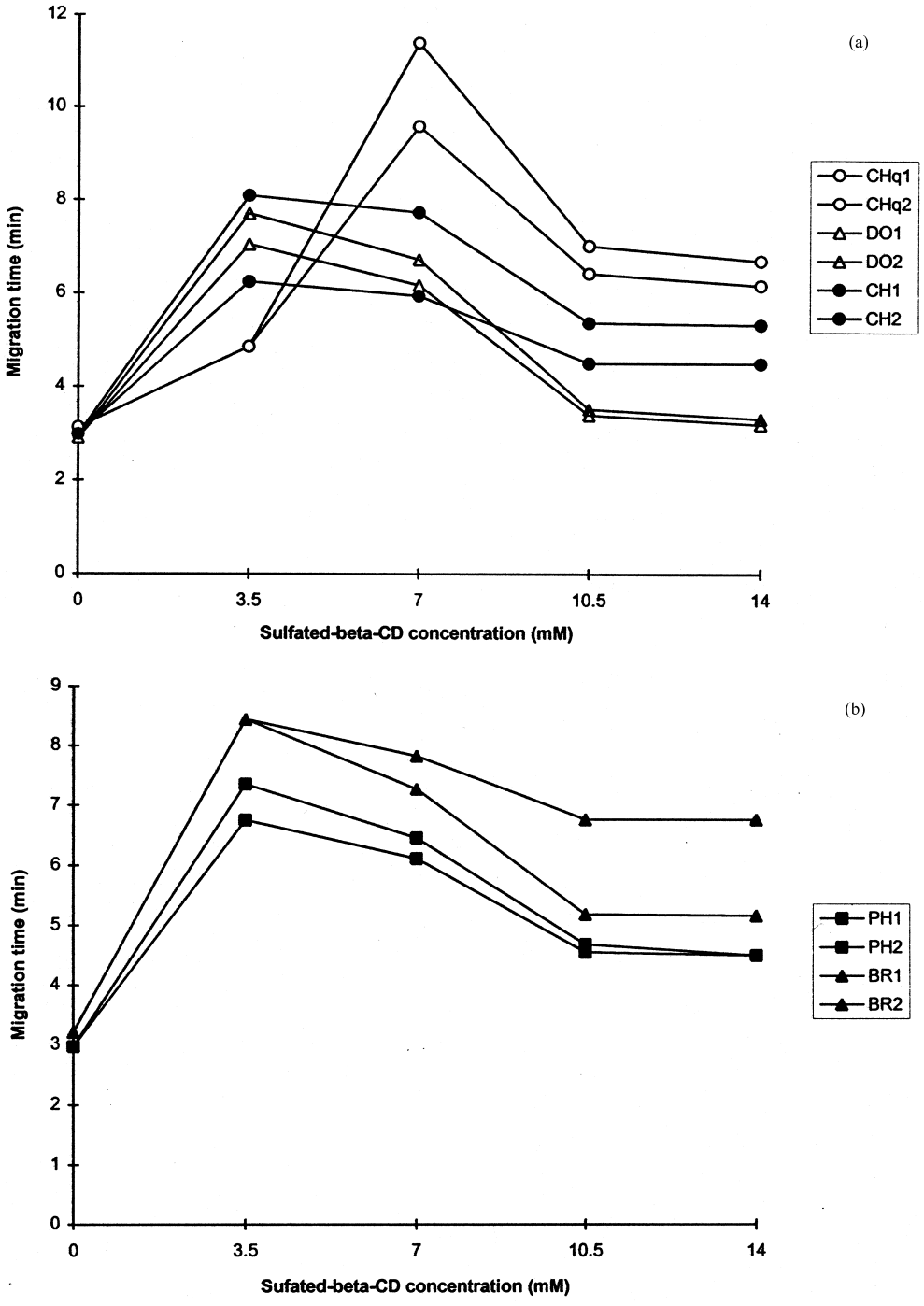

Fig. 2. Effect of sulfated-β-CD concentration on migration time and resolution of the compounds studied. Capillary 53 (30) cm×75 μm I.D. fused-silica; BGE, 10 m*M* phosphate at pH 3.84 with different concentrations of CD; applied voltage, 12.4 kV; hydrostatic injection (25 s); sample concentration, approximately 100 ppm each. ■=(±)-Pheniramine (PH1 and PH2), ●=(±)-chlorpheniramine (CH1 and CH2), ▲=(±)-brompheniramine (BR1 and BR2), △=(±)-doxylamine (DO1 and DO2), ○=(±)-chloroquine (CHq1 and CHq2).

mine and (±)-doxylamine reached maximum as the concentration of sulfated-β-CD increased to ~3.5 m*M* (0.5%, w/v). Further increase of sulfated-β-CD concentration to ~14 m*M* (2%, w/v) decreased the migration times and resolution. The migration times and resolution of (±)-chloroquine reached maximum at a concentration of ~7 m*M* (1%, w/v) sulfated-β-CD. Further increase of sulfated-β-CD concentration caused a decrease in the migration times and resolution. The racemic brompheniramine behaved differently from the above four compounds. When the concentration of sulfated-β-CD increased to ~3.5 m*M* (0.5%, w/v), the migration time of (±)-brompheniramine reached a maximum, but no separation was observed. Further increase of sulfated-β-CD to ~14 m*M* (2%, w/v) decreased the migration time and resolution increased significantly. It was found that five of the compounds studied were all resolved when ~7 m*M* (1%, w/v) sulfated-β-CD was added to the background electrolyte (BGE).

3.1.2. Effects of pH on migration and resolution

In order to verify the influence of pH on the resolution of the enantiomers studied, experiments were performed with ~7 m*M* (1%, w/v) sulfated-β-CD at pH 2.8, 3.8, 4.8 and 5.8. The effects of pH on migration time and resolution are shown in Fig. 3. In general, the migration time and resolution decreased as pH increased. This result was in accordance with the fact that EOF was enhanced with the increase in pH value. Presumably, at high pH, the EOF is stronger than the electrophoretic flow, thus the net migration of sulfated-β-CD may be in the direction of the cathode [20]. Therefore, both of the analytes and sulfated-β-CD may migrate towards the cathode and the difference of binding constants becomes smaller leading to the decreased resolution. At pH 2.8, no peaks were observed for all the enantiomers studied within 15 min with a serious baseline drift. This result is probably due to the suppress of EOF and reverse migration of analytes interacting with sulfated-β-CD which is migrating towards the anode. At pH 3.8, all of the analytes were well resolved. At pH 4.8, pheniramine was only partially resolved although satisfactory separation was achieved for the other four analytes. Chiral resolution was lost for pheniramine at pH 5.8. Thus, pH 3.8 was found to be optimal. Optimized separation conditions were chosen as ~7 m*M* (1%, w/v) sulfated-β-CD at pH 3.8. Typical electropherograms obtained using these conditions are illustrated in Fig. 4. Sulfated-β-CD proved to be an efficient chiral selector under appropriate experimental conditions. But separation of the three analytes, i.e., (±)-pheniramine, (±)-brompheniramine, (±)-chlorpheniramine, in a single run was not possible since they comigrated. It should be noted that owing to the negative charge of the sulfate group, the ionic strength of the run buffer increased significantly and thus limited the use of higher voltage because of the increase in Joule heating effect [4].

Baseline separation conditions were obtained for each of the five analytes by addition of ~7 m*M* (1%, w/v) sulfated-β-CD into the BGE at pH 3.84. Due to comigration, (±)-pheniramine, (±)-chlorpheniramine and (±)-brompheniramine could not be separated in one run.

3.2. CE-β-CD and HP-β-CD as chiral selectors

Two other CDs, CE-β-CD and HP-β-CD were employed to separate five basic drugs. Carboxylic acid groups most likely have a pK_a value of 4–5 and thus some fractional ionization will be expected at pH value less than 4 [21]. They deprotonate and become anionic at higher pH (>5) [6,21]. When experiments were performed at lower pH (2.7 and 3.8), no peaks were observed for all the five compounds. In this situation, EOF is suppressed and the analytes are positively charged, and hence migration should have been observed unless complexation with the CD occurred and the CD was negatively charged thus leading to a reversal in migration. When the experiments were performed at higher pH (4.8, 5.8), chiral recognition was obtained for three and four of the compounds, respectively, i.e., (±)-pheniramine, (±)-chlorpheniramine, (±)-brompheniramine and (±)-doxylamine by addition of 14 m*M* (2%, w/v) CE-β-CD. Separation of (±)-brompheniramine was not achieved at pH 4.8. Fig. 5a,b show the electropherograms obtained at pH 5.8. (±)-Pheniramine and (±)-doxylamine comigrated and could not be separated in one run while separation of three analytes, (±)-pheniramine, (±)-chlorpheniramine and (±)-brompheniramine in one run was successfully achieved. Throughout the experiment uncoated

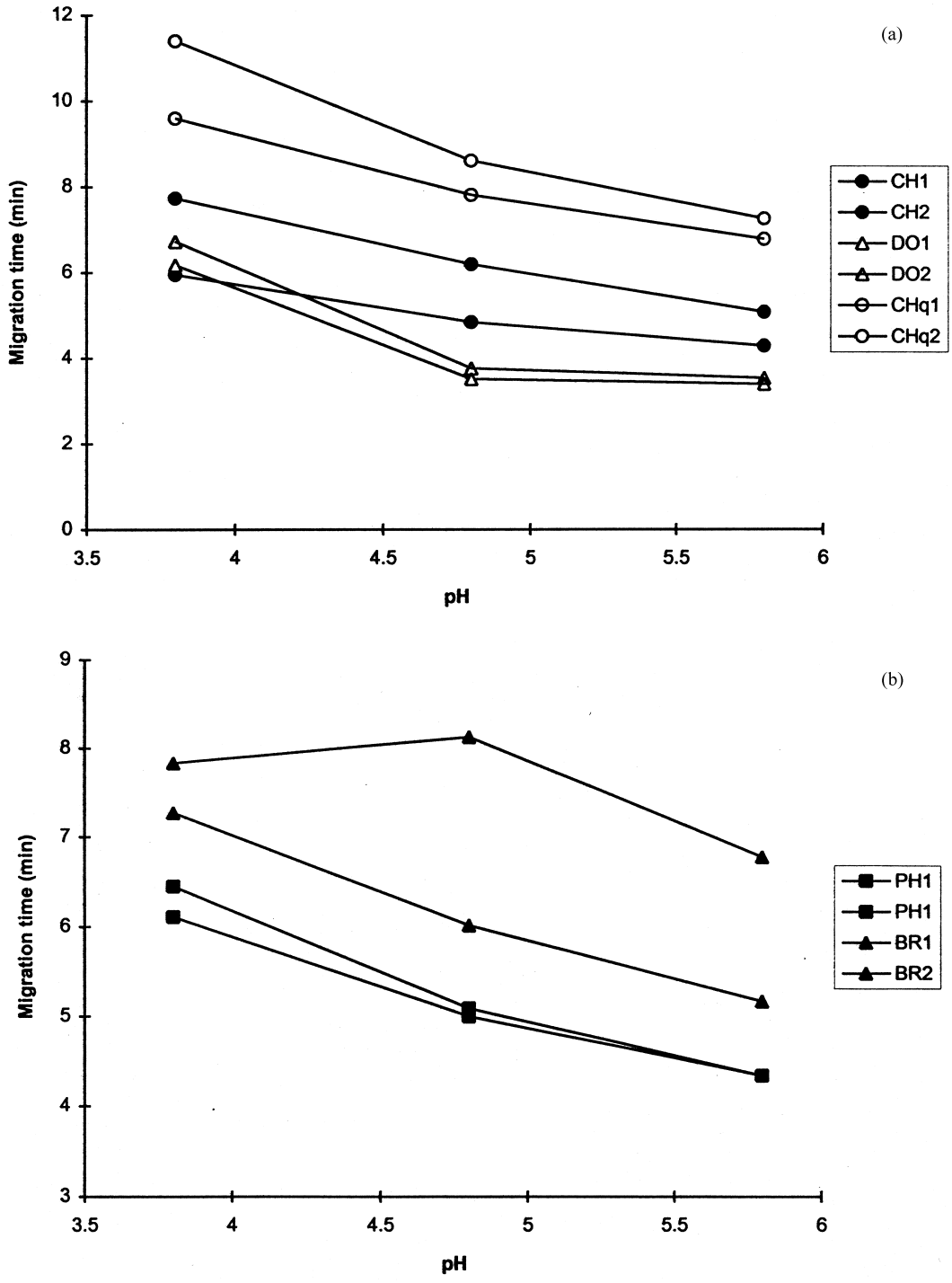

Fig. 3. Effect of buffer pH on migration time and resolution of the compounds studied. ~7 m*M* (1%, w/v) sulfated-β-CD concentration at different pH, other experimental conditions and symbols as in Fig. 2.

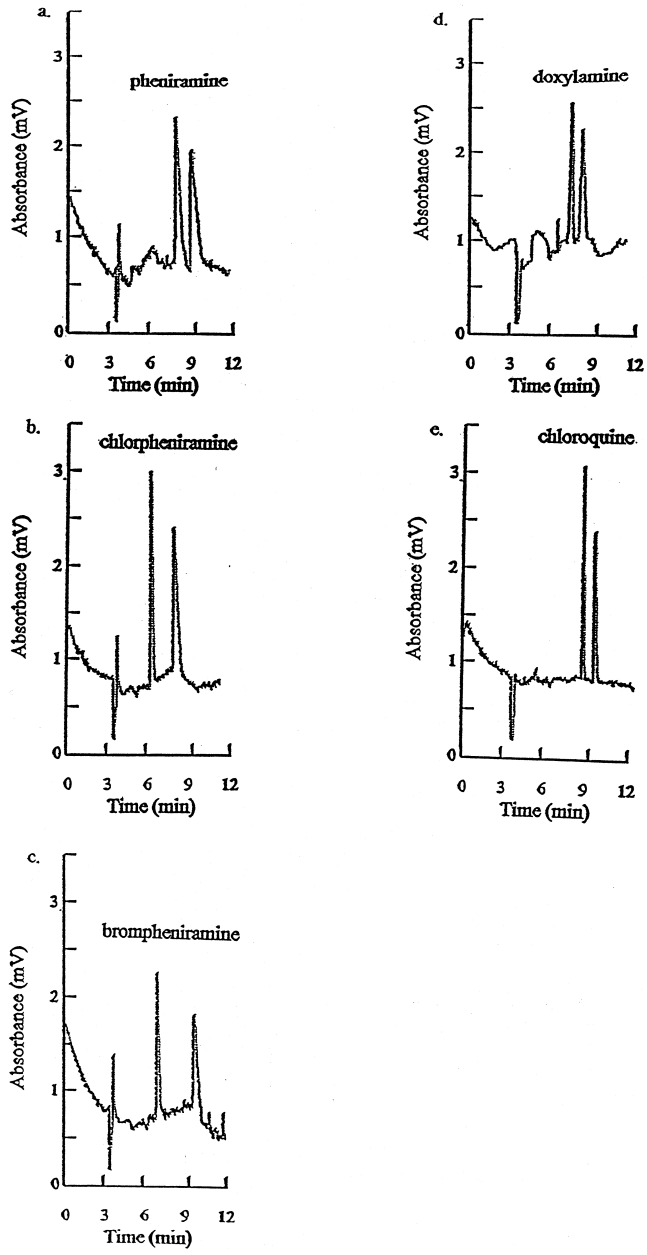

Fig. 4. Electropherograms of enantiomeric separation of five compounds by sulfated-β-CD. (a–e) Capillary 57 (34) cm×75 μm I.D. fused-silica; ~7 m*M* (1%, w/v) sulfated-β-CD at pH 3.84; applied voltage, 12.4 kV; other experimental conditions as in Fig. 2.

capillary was used. Perhaps due to the high viscosity of the buffer electrolyte with 14 m*M* (2%, w/v) of CE-β-CD, the EOF was moderately suppressed. Hence, at pH 5.8, the anionic CE-β-CD migrated towards the anode while the analytes which were positively charged migrated towards the cathode, thus leading to successful separation.

HP-β-CD resolved only (±)-chlorpheniramine and (±)-brompheniramine at a concentration of 28 m*M* (4%, w/v), pH 3.2 (Fig. 6). Higher concen-

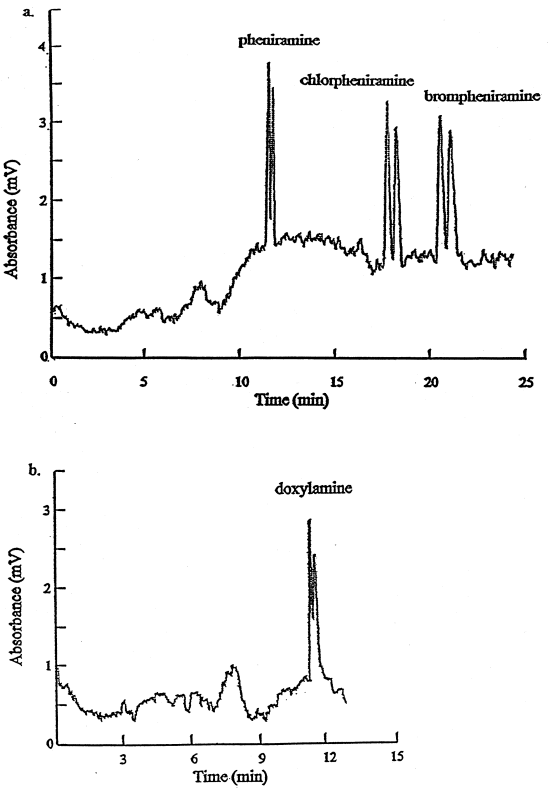

Fig. 5. Electropherograms of enantiomeric separation of four compounds by CE-β-CD. Capillary 57 (34) cm×75 μm I.D., fused-silica; BGE, 20 m*M* phosphate at pH 5.8, 14 m*M* (2%, w/v) CE-β-CD; applied voltage, 13 kV; hydrostatic injection (15 s); sample concentration, 100 ppm each.

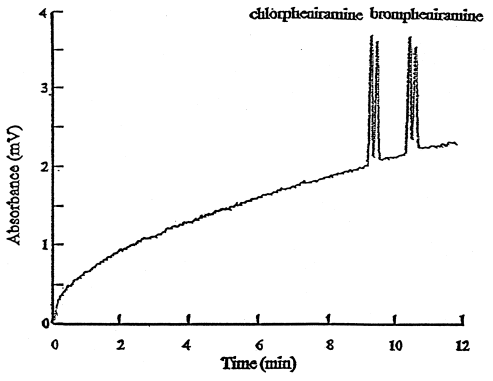

Fig. 6. Electropherograms of enantiomeric separation of two compounds by HP-β-CD. BGE, 50 m*M* phosphate at pH 3.24, 28 m*M* (4%, w/v) HP-β-CD; Other experimental conditions as in Fig. 5.

tration was required to resolve these two racemic compounds. Armstrong et al. [22] reported a larger k' for bromide ion than for chloride ion on a β-CD column. Thus, the halide substituent may contribute to the formation of an inclusion complex between the analyte and the CD cavity [8]. Due to its neutrality, it did not contribute to the ionic strength of the buffer. Therefore, the baseline was relatively stable.

3.3. Effect of structures of CDs on the resolution

In order to understand the chiral recognition capabilities of different CDs, a knowledge of the differences in their structures is necessary. Naturally occurring CDs, i.e., α-, β- and γ-CD are composed of six, seven and eight glucose units, each has three hydroxyl groups at positions 2, 3 and 6 which can be substituted by different functional groups. The substituent groups of commonly used CDs are tabulated in Table 1. R^2, R^3 and R^6 (see Table 1) represent the substituent at position 2, 3 and 6 in each of glucose unit. The average degree of substitution (DS) for sulfated-β-CD is 7–10, but exact substitution pattern is unknown. The situation is the same for β-CD-SBE(IV) (DS, ~4), CM-β-CD (DS, ~3.6), CE-β-CD (DS, ~3 and ~6) and HP-β-CD (DS, 0.6 and 0.8). Although these substituents are tabulated at R^2 position, it does not necessarily mean that the substitution really occurred at this position. The substitution pattern of di-OMe-β-CD and tri-OMe-β-CD is known to be at positions 2 and 6 and 2, 3 and 6, respectively. The degree of substitution is only given by an average value because modified CDs are complexed mixtures with different substitution degrees.

In this work, sulfated-β-CD, CE-β-CD and HP-β-CD were examined for their chiral recognition capabilities. Sulfated-β-CD (DS, 7–10) gave resolution to all the five analytes studied. Although the exact substitution pattern was unknown, it is assumed that at least one hydroxyl group was substituted by sulfate group in each of glucose unit which could form ion-pairs with cationic enantiomers due to Coulombic interactions which assisted chiral recognition. Due to the reverse migration of anionic sulfated-β-CD to the cationic analytes, the counter-current mobility thus formed allows for a smaller

Table 1
Cyclodextrins and their substituents

Abbreviation	R^2	R^3	R^6	DS (molecules per CD ring)
Sulfated-β-CD	SO_3^-	H	H	7–10
β-CD-SBE (IV)	$(CH_2)_4SO_3^-$	H	H	~4
CM-β-CD	CH_2COOH	H	H	~3.6
CE-β-CD	CH_2CH_2COOH	H	H	~3 and ~6
HP-β-CD	$CH_2CH_2CH_2OH$	H	H	~0.6 and ~0.8
di-OMe-β-CD	CH_3	H	CH_3	~14
tri-OMe-β-CD	CH_3	CH_3	CH_3	~21

difference in interaction constants leading to the successful resolution of the enantiomers.

The degree of substitution of CE-β-CD (DS, ~3 in this work) is lower than that of sulfated-β-CD. Therefore, the overall negative charge of CE-β-CD is less than that of sulfated-β-CD, and the overall chiral recognition capability of CE-β-CD is not as good as that of sulfated-β-CD. HP-β-CD (DS, ~0.8 in this work) is neutral and behaves as a quasi-stationary phase at all pH, and hence counter migration between chiral selectors and analytes does not happen. Neither do ion-pairing effects. Thus, its chiral recognition capability is not as significant as the anionic one.

The resolution values of five compounds obtained by using three CDs are tabulated in Table 2. It is apparent that the negatively charged sulfated-β-CD and CE-β-CD resolved more racemic compounds than neutral HP-β-CD. In addition, less amounts of negatively charged CDs were required for the chiral separation. It should be noted that sulfated-β-CD could not simultaneously separate (±)-pheniramine, (±)-chlorpheniramine and (±)-brompheniramine whereas CE-β-CD gave satisfactory separation of three compounds in one run.

Table 2
Resolution (R')[a] of the five compounds obtained using sulfated-β-CD, CE-β-CD and HP-β-CD as chiral selectors

Compound	R'		
	~7 m*M* (1%) sulfated-β-CD	14 m*M* (2%) CE-β-CD	28 m*M* (4%) HP-β-CD
Pheniramine	100	85	–
Chlorpheniramine	100	96	95
Brompheniramine	100	90	89
Doxylamine	100	57	–
Chloroquine	100	–	–

[a] Resolution, R',=100($H-H_3$)/H with $H=(H_1+H_2)/2$, where H_1, H_2 and H_3 are the heights of the first peak, the second peak and the valley between the two peaks, respectively. An R' value of 100 represents a baseline separation of the enantiomers [13].

3.4. Qualitative analysis of pharmaceutical formulations

Two samples containing approximately 100 ppm chlorpheniramine and chloroquine were analysed using 10 m*M* phosphate (pH 3.82) with ~7 m*M* (1%, w/v) sulfated-β-CD as the buffer additive. The electropherograms (see Fig. 7) showed the presence of the two enantiomers in both samples, indicating

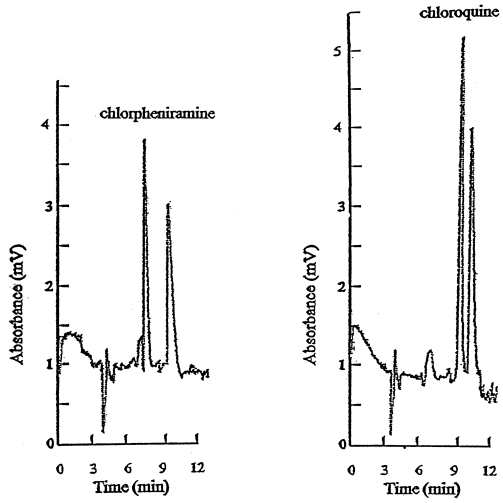

Fig. 7. Electropherograms of enantiomeric separation of two drug samples by sulfated-β-CD. Capillary 57 (34) cm×75 μm I.D. fused-silica; BGE, 10 m*M* phosphate at pH 3.82, ~7 m*M* (1%, w/v) sulfated-β-CD; applied voltage, 12.4 kV; hydrostatic injection (25 s); sample concentration, approximately 100 ppm each.

that the two drugs are administered in racemic forms. Further confirmation was made by spiking the two samples with standard mixtures containing racemic chlorpheniramine and chloroquine.

4. Conclusions

Chiral resolution of basic racemic compounds with neutrally and negatively substituted CDs as chiral selectors depends on several parameters. The structure of the CD is vital to the chiral recognition capability of this group of chiral selectors. The type of substituent and the degree of substitution on the rim of CD determine its countercurrent mobility and ion-pairing effect which are the main driving forces in the successful chiral resolution. The optimization of parameters such as chiral selector concentration and buffer pH is also very crucial in successful chiral resolution.

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