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Enantioseparation of phenothiazines in capillary zone electrophoresis using cyclodextrins as chiral selectors

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Abstract

In this study, enantioseparations of five phenothiazines, including promethazine, ethopropazine, trimeprazine, methotrimeprazine, and thioridazine, in cyclodextrin (CD)-modified capillary zone electrophoresis were investigated using a phosphate buffer (40 m*M*) at pH 3.0. We focussed on the separation of phenothiazines with the use of CDs at low concentrations. Three different CDs, including β-CD, hydroxypropyl-β-CD (HP-β-CD) and γ-CD, were chosen as chiral selectors. The results indicate that effective enantioseparation of phenothiazines, except for methotrimeprazine, is simultaneously achievable with addition of γ-CD at a concentration of 2.5–6.0 m*M*. The enantiomers of ethopropazine and trimeprazine are effectively separated with addition of HP-β-CD at low concentrations, in the range 0.4–6.0 m*M*, whereas those of promethazine and trimeprazine are baseline resolved with β-CD at much lower concentrations (0.02–3.0 m*M*) than with HP-β-CD. The results also confirm that the separation window is greatly enlarged at low CD concentrations. Moreover, the drastic variations of the electrophoretic mobility of phenothiazines as a function of CD concentration reveal that phenothiazines interact very strongly with CDs in the order γ-CD<HP-β-CD<β-CD.

Keywords: Enantiomer separation; Pharmaceutical analysis; Phenothiazines; Cyclodextrins; Organosulfur compounds

1. Introduction

Phenothiazines are generally used as antipsychotic and neuroleptic agents. Potentially useful phenothiazine derivatives have different substituents attached at the 2-position (R_2) and 10-position of the phenothiazine ring (R_{10}) with an alkyl piperazine group or an aliphatic side chain containing an amino group [1]. Among them, promethazine, ethopropazine, trimeprazine, methotrimeprazine, and thioridazine possess a chiral center. Fig. 1 depicts the structures of the phenothiazines studied.

During the past two decades, separation of the enantiomers of phenothiazines has usually been performed by high-performance liquid chromatography (HPLC) [2–7]. In recent years, applications of capillary electrophoresis (CE) to the chiral separation and/or determination of pharmaceutical compounds have become popular and have attracted the attention of many researchers [8–14]. This is due to the many advantageous features of CE, such as its extremely high efficiency, high resolution, rapid analysis and small consumption of sample, in comparison with HPLC [15–18].

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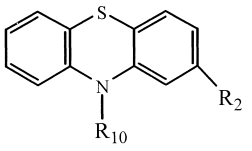


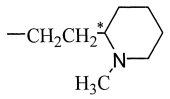
	R_2	R_{10}
Promethazine (**1**)	H	$-CH_2\overset{*}{C}H(CH_3)N(CH_3)_2$
Ethopropazine (**2**)	H	$-CH_2\overset{*}{C}H(CH_3)N(C_2H_5)_2$
Trimeprazine (**3**)	H	$-CH_2\overset{*}{C}H(CH_3)CH_2N(CH_3)_2$
Methotrimeprazine (**4**)	OCH_3	$-CH_2\overset{*}{C}H(CH_3)CH_2N(CH_3)_2$
Thioridazine (**5**)	SCH_3	

Fig. 1. Structures of the phenothiazines studied.

Applications of the CE technique to the separation of phenothiazines have previously been demonstrated using either micellar electrokinetic chromatography [19,20] or capillary zone electrophoresis (CZE) [20–24]. However, only three articles have appeared in the literature regarding the applications of the CE technique to the enantioseparation and/or determination of phenothiazines [22–24]. The enantiomers of promethazine were separated by CZE with albumin as chiral selector using a phosphate buffer at pH 7.6 [22,23]. Enantioseparation of trimeprazine has been demonstrated with addition of hydroxypropyl-β-cyclodextrin (HP-β-CD) (8–22 m*M*) to a phosphate buffer (100 m*M*) at pH 2.5 and at 15.5°C [24]. Thus, understanding of the enantioseparation of phenothiazines in CZE is rather incomplete or even lacking. Obviously, a systematic and more thorough investigation of the chiral separation of phenothiazines is desirable. In this report, three different cyclodextrins (CDs), including β-CD, HP-β-CD and γ-CD, were selected as chiral selectors with an emphasis on the separation of five phenothiazines using CDs at low concentrations. The variations of the electrophoretic mobility of phenothiazines as a function of CD concentration at pH 3.0 were examined. Here we present the results of the investigation.

2. Experimental

2.1. Apparatus

All CE separations were performed on a Beckman P/ACE System MDQ with a photodiode array detector for absorbance measurements at 240 nm (Beckman Coulter, Fullerton, CA, USA). Uncoated fused-silica capillaries purchased from Polymicro Technologies (Phoenix, AZ, USA) were used. The dimensions of the capillary were 60.2 cm×50 μm I.D. The effective length of the capillary was 50 cm from the injection end of the capillary. The CE system was interfaced with a microcomputer and a laser printer. System Gold software of Beckman was used for data acquisition. For pH measurements, a pH meter (Suntex Model SP-701, Taipei, Taiwan) was employed with a precision of ±0.01 pH unit.

2.2. Chemicals and reagents

The five phenothiazines were obtained from Sigma (St. Louis, MO, USA). All other chemicals were of analytical grade. Deionized water was prepared with a Milli-Q system (Millipore, Bedford, MA. USA).

Standard solutions of the phenothiazines at a concentration of 10 μg/mL were prepared by dissolving analytes in an aqueous solution. The pH of a phosphate buffer was adjusted to the desired pH value by mixing various proportions of a certain concentration of trisodiumphosphate solution with the same concentration of phosphoric acid. All buffer solutions, freshly prepared weekly and stored in a refrigerator before use, were filtered through a membrane filter (0.22 μm).

2.3. Electrophoretic procedure

When a new capillary was used, the capillary was washed 30 min with 1.0 *M* NaOH solution, followed by 30 min with deionized water at 25°C. Before each injection, the capillary was prewashed for 3 min with running buffer and postwashed for 3 min with deionized water, 3 min with 0.1 *M* NaOH, and 5 min with deionized water to maintain proper reproducibility of run-to-run injections. Sample injections were done in a hydrodynamic mode over 5 s under a pressure of 1.0 p.s.i. at 25°C. The measurements

were run at least in triplicate to ensure reproducibility. An applied voltage of 20 kV for the phosphate buffer was selected to keep the total current less than 100 μA in order to avoid experimental complications resulting from Joule heating. The detection wavelength was set at 240 nm. Peak identification was conducted by spiking with the analyte to be identified. Mesityl oxide was used as a neutral marker. The relative standard deviation of the migration time is less than 0.6% ($n=5$).

2.4. Mobility calculations

The electrophoretic mobility of analytes was calculated from the observed migration times using the equation:

$$\mu_{ep} = \mu - \mu_{eo} = \frac{L_d L_t}{V} \cdot \left(\frac{1}{t_m} - \frac{1}{t_{eo}} \right)$$

where μ_{ep} is the electrophoretic mobility of the analyte tested, μ is the apparent mobility, μ_{eo} is the electroosmotic mobility, t_m is the migration time measured directly from the electropherogram, t_{eo} is the migration time for an unchanged solute, L_t is the total length of the capillary, L_d is the length of capillary between injection and detection, and V is the applied voltage.

3. Results and discussion

It has been demonstrated that the addition of HP-β-CD to the electrophoretic system can enlarge the separation window so that better separability and greater selectivity of phenothiazines can be obtained [24]. Accordingly, the extent of the separation window, which is governed by the concentration of CD, depends on the extent of the complexation between phenothiazines and CDs.

3.1. Enantioseparation of phenothiazines with addition of HP-β-CD

The variation of the electrophoretic mobility of phenothiazine enantiomers as a function of HP-β-CD concentration in the range 0–8 m*M* using a phosphate buffer (40 m*M*) at pH 3.0 was investigated. The electrophoretic mobility of each individual phenothiazine was found to decrease drastically with increasing HP-β-CD concentration, especially in the region 0–3 m*M*. This phenomenon reveals that phenothiazines interact strongly with HP-β-CD. The greater the extent of the variation of electrophoretic mobility, the stronger the interaction between phenothiazines and HP-β-CD. Thus, the interaction between the five phenothiazines and HP-β-CD increases in the order promethazine < ethopropazine < trimeprazine < methotrimeprazine < thioridazine. Since trimeprazine migrates faster than ethopropazine toward the cathode in CZE separation in the absence of HP-β-CD at pH 3.0, the reversal of the migration order of trimeprazine and ethopropazine occurs upon the addition of HP-β-CD to the background electrolyte at pH 3.0.

Effective enantioseparation of ethopropazine and trimeprazine was achieved with addition of HP-β-CD at a concentration in the range 0.4–8.0 m*M* and 0.1–6.0 m*M*, respectively, in a phosphate buffer at pH 3.0. However, the enantiomers of thioridazine could only be resolved with HP-β-CD at a concentration of less than 0.2 m*M*. For illustration, Fig. 2A–F show some typical electropherograms of these phenothiazines with HP-β-CD at 0.1, 0.4, 1.2, 2.5, 6.0 and 8.0 m*M*, respectively. The enantiomers of trimeprazine and thioridazine were baseline separated with addition of 0.1 m*M* HP-β-CD (Fig. 2A); complete enantioseparation of ethopropazine was achieved with HP-β-CD at 0.4 m*M* (Fig. 2B). Under the circumstances of baseline separation of the two enantiomers, the enantioselectivity of trimeprazine increased with increasing HP-β-CD concentration from 0.1 to 1.2 m*M* (Fig. 2C), but decreased with further increasing HP-β-CD concentration from 1.2 to 6.0 m*M* (Fig. 2E). The peaks between the two enantiomers of trimeprazine were not resolvable at all when the HP-β-CD concentration exceeded 15 m*M* [25]. Similarly, the enantioselectivity of ethopropazine also increased with increasing HP-β-CD concentration from 0.1 to 1.2 m*M*, but to a lesser extent than that of trimeprazine; it then decreased with further increasing the HP-β-CD concentration from 1.2 to 8.0 m*M*, while keeping the two enantiomers of ethopropazine baseline separated (Fig. 2F). On the other hand, the two enantiomers of promethazine were barely resolved with addition of HP-β-CD at a concentration in the range 1.6–4.0

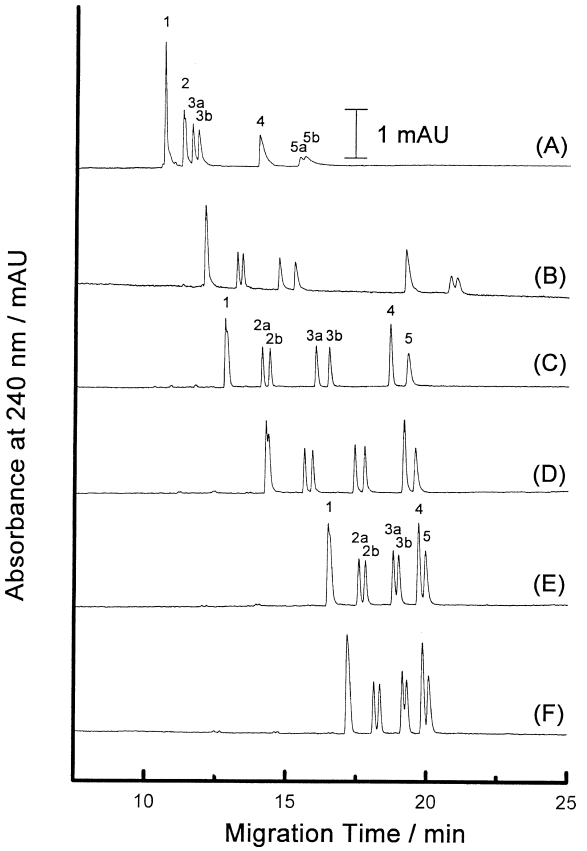


Fig. 2. Electropherograms of the phenothiazines obtained with 40 m*M* phosphate buffer containing varied concentration of HP-β-CD at pH 3.0: (A) 0.1 m*M*, (B) 0.4 m*M*, (C) 1.2 m*M*, (D) 2.5 m*M*, (E) 6.0 m*M*, (F) 8.0 m*M*. Peak identification: 1=promethazine, 2=ethopropazine, 3=trimeprazine, 4=methotrimeprazine, 5=thioridazine.

m*M*, although the separability was slightly improved at about 2.5 m*M* (Fig. 2D). However, as observed previously by Boer et al. with HP-β-CD at concentrations greater than 8 m*M* [24], no enantioseparation of methotrimeprazine could be achieved with HP-β-CD at any concentration in the range 0–8.0 m*M*.

The separation window is greatly enlarged with addition of HP-β-CD, especially at low HP-β-CD concentrations (0–3 m*M*). Thus, for better enantioseparability and greater enantioselectivity of phenothiazines, the use of HP-β-CD at low concentrations ($<$8 m*M*) is more advantageous than at the relatively higher concentrations employed by Boer et al. [24]. The optimal concentration ranges of HP-β-CD for enantioseparation of ethopropazine and trimeprazine were found to be 0.4–8.0 and 0.1–6.0 m*M*, respectively.

With HP-β-CD as a chiral selector, chiral recognition of the enantiomers of ethopropazine and trimeprazine is apparently related to an appropriate arrangement of the chain lengths between the aliphatic side chain of phenothiazines (chiral selectands) and the hydroxypropyl group of HP-β-CD (chiral selector). This arrangement may involve a hydrogen bonding interaction between the tertiary amino group of phenothiazines and the hydroxypropyl group of HP-β-CD located at the rim of the CD cavity. Similar arguments are also applicable to chiral recognition of promethazine and trimeprazine with the use of β-CD, which will be discussed in Section 3.2.

By comparing the structure of methotrimeprazine with that of trimeprazine, we believe that enantioseparation of methotrimeprazine with HP-β-CD is hindered when the 2-position of the phenothiazine ring contains a methoxy group. Apparently, the hydrogen bonding interaction between the aliphatic side chain (R_{10}) of methotrimeprazine and the hydroxylpropyl group of HP-β-CD located at the rim of the CD cavity is greatly reduced.

3.2. Enantioseparation of phenothiazines with addition of β-CD

The variation of the electrophoretic mobility of phenothiazine enantiomers as a function of β-CD concentration in the range 0–6 m*M* under the same electrophoretic conditions as in the case of HP-β-CD was examined. The variation of the electrophoretic mobility of phenothiazines was similar to that when HP-β-CD was used. More effective enantioseparation of promethazine and trimeprazine, but with no enantioseparation of ethopropazine, was noted. The enantiomers of thioridazine could be resolved with β-CD only in a very limited concentration range ($<$0.3 m*M*). Obviously, a stronger interaction of each individual phenothiazine with β-CD than with HP-β-CD is occurring. In fact, the binding constants of phenothiazines to β-CD are about 2.5- to threefold greater than those of phenothiazines to HP-β-CD [25].

Effective enantioseparation of promethazine and trimeprazine was achieved with addition of β-CD at a concentration in the range 0.3–2.0 and 0.02–2.0 m*M*, respectively. However, no enantioseparation of ethopropazine and methotrimeprazine could be achieved. The optimal concentration of β-CD for enantioseparation of trimeprazine was surprisingly small. In comparison with the results obtained with HP-β-CD, this result could not be rationalized simply based on the binding strength of trimeprazine with β-CD alone. Further investigation is needed.

For illustration, Fig. 3A–F show some typical electropherograms of these phenothiazines with β-CD at 0.02, 0.05, 0.1, 0.3, 2.0, and 6.0 m*M*, respectively. The enantiomers of trimeprazine were baseline separated with addition of β-CD at a concentration as low as 0.02 m*M* (Fig. 3A). With β-CD at this concentration, ethopropazine and trimeprazine were not completely separated. However, as shown in the attachment of Fig. 3A, effective enantioseparation of trimeprazine was achieved when trimeprazine alone was injected into the capillary column. The enantioselectivity of trimeprazine, while keeping the two enantiomers baseline separated, increased with increasing β-CD concentration, similar to the case with HP-β-CD, reaching its maximum value at 0.3 m*M* (Fig. 3D), and then decreased with increasing β-CD concentration from 0.3 to 2.0 m*M* (Fig. 3E). Beyond 2.0 m*M*, the resolution of the peaks between the two enantiomers of trimeprazine decreased. The enantiomers of trimeprazine became unresolvable when the β-CD concentration exceeded 6.0 m*M* (Fig. 3F). On the other hand, the enantioseparation of thioridazine could be achieved with β-CD only in the concentration range 0.05–0.3 m*M* (Fig. 3B–D). The enantiomers of promethazine were partially resolved with β-CD at 0.1 m*M* (Fig. 3C); complete enantioseparation of promethazine was achieved with β-CD at 0.3 m*M* (Fig. 3D). Similarly, the enantioselectivity of promethazine increased with increasing β-CD concentration, but to a slightly lesser extent than that of trimeprazine. The enantioselectivity of promethazine reached its maximum value at about 1.0 m*M*, then decreased with increasing β-CD concentration from 1.0 to 2.0 m*M*, while keeping the two enantiomers of promethazine baseline separated (Fig. 3E).

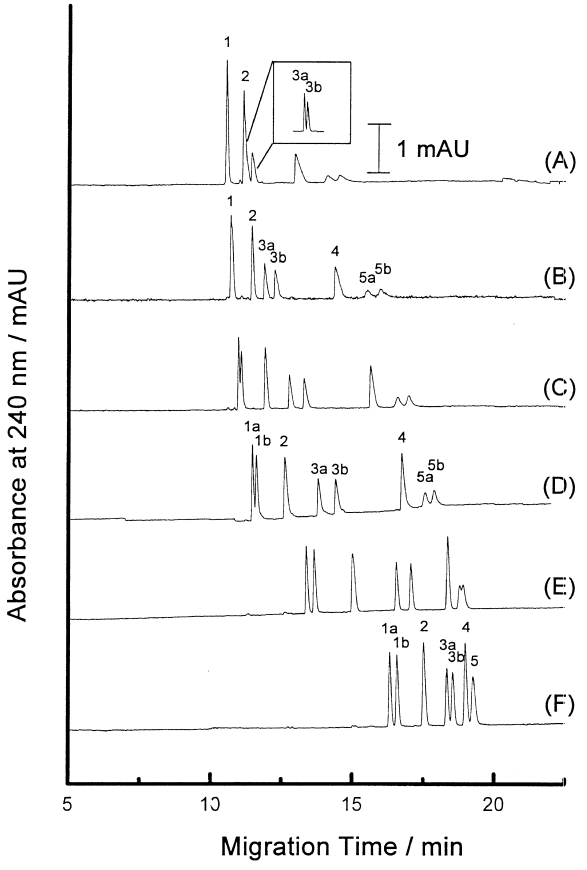


Fig. 3. Electropherograms of the phenothiazines obtained with 40 m*M* phosphate buffer containing varied concentration of β-CD at pH 3.0: (A) 0.02 m*M*, (B) 0.05 m*M*, (C) 0.1 m*M*, (D) 0.3 m*M*, (E) 2.0 m*M*, (F) 6.0 m*M*. Peak identification as for Fig. 2.

The structures of inclusion complexes of β-CD with phenothiazine derivatives were examined theoretically using computer graphic modeling [3] and molecular dynamics calculation [26]. It was suggested that approximately one-half of the phenothiazine ring was embedded in the cavity of β-CD and that the other half of the phenothiazine ring, together with the R_2 and R_{10} substituents, was located outside the cavity of β-CD [26]. Accordingly, a hydrogen bond might be formed between the nitrogen atom of the aliphatic side chain (R_{10}) and the hydroxyl group of β-CD located at the rim of the β-CD cavity [3,26]. Thus the results obtained in this work reveal that the hydrogen bonding interaction should play an important role in chiral discrimination of the enantiomers of phenothiazines. By comparing the structure

of ethopropazine with those of promethazine and trimeprazine, it is thought that, owing to the bulky nature of the tertiary diethylamino group in ethopropazine, the formation of a hydrogen bond between the aliphatic side chain containing an amino group in ethopropazine and the hydroxy group of β-CD located at the rim of the β-CD cavity is considerably reduced or even prevented, thus leading to the failure of chiral recognition of ethopropazine.

3.3. Enantioseparation of phenothiazines with addition of mixed CDs

As described in Section 3.2, effective enantioseparation of promethazine and trimeprazine was simultaneously achieved with addition of 0.3–6.0 m*M* β-CD to a phosphate buffer (40 m*M*) at pH 3.0. On the other hand, as described in Section 3.1, the enantiomers of ethopropazine and trimeprazine were effectively and simultaneously separated with addition of 0.4–2.0 m*M* HP-β-CD to the same background electrolyte. Thus, we thought that complete enantioseparation of promethazine, ethopropazine and trimeprazine might be simultaneously achievable with addition of mixed CDs composed of β-CD and HP-β-CD. In fact, by fixing the β-CD concentration at 0.3 m*M* and varying the HP-β-CD concentration from 0.4 to 2.0 m*M*, the resolution of the two enantiomer peaks of ethopropazine can progressively be improved as the concentration of HP-β-CD increases. Complete enantioseparation of these three phenothiazines was successfully achieved with addition of mixed CDs composed of 0.3 m*M* β-CD and 1.4 m*M* HP-β-CD. Fig. 4 shows such an electropherogram of the phenothiazines obtained.

3.4. Enantioseparation of phenothiazines with addition of γ-CD

The variation of the electrophoretic mobility of phenothiazine enantiomers as a function of γ-CD concentration in the range 0–10 m*M* using the same phosphate buffer at pH 3.0 as in the case of HP-β-CD was studied. The variation of the electrophoretic mobility of phenothiazines was similar to that with HP-β-CD, but not as drastic. Effective enantioseparation of promethazine, ethopropazine, trimeprazine,

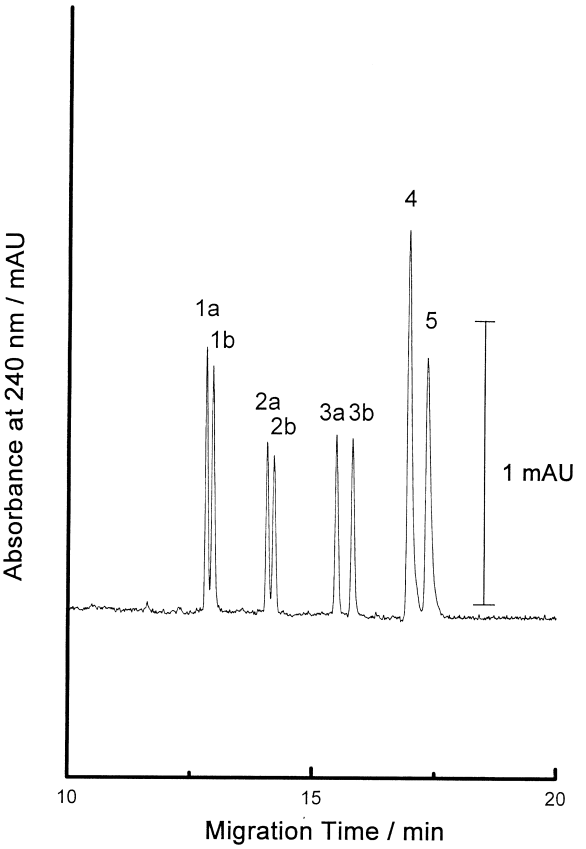


Fig. 4. Electropherograms of phenothiazines obtained with 40 m*M* phosphate buffer containing a mixed CD composed of 0.3 m*M* β-CD and 1.4 m*M* HP-β-CD at pH 3.0. Peak identification as for Fig. 2.

and thioridazine, but not of methotrimeprazine, was achieved. In comparison with the results obtained in Fig. 2, the less drastic change in the electrophoretic mobility as a function of γ-CD concentration reveals that the interaction of phenothiazine is comparatively weaker with γ-CD than with HP-β-CD. This is probably due to the loose fit of the size of phenothiazines to the cavity of γ-CD. The binding constants of phenothiazines to β-CD are about 4.5- to ninefold smaller than those of phenothiazines to HP-β-CD [25].

Effective enantioseparation of promethazine, ethopropazine, trimeprazine, and thioridazine was achieved with addition of γ-CD at a concentration in the range 2.5–10.0, 1.6–10.0, 2.5–6.0 and 0.1–10.0

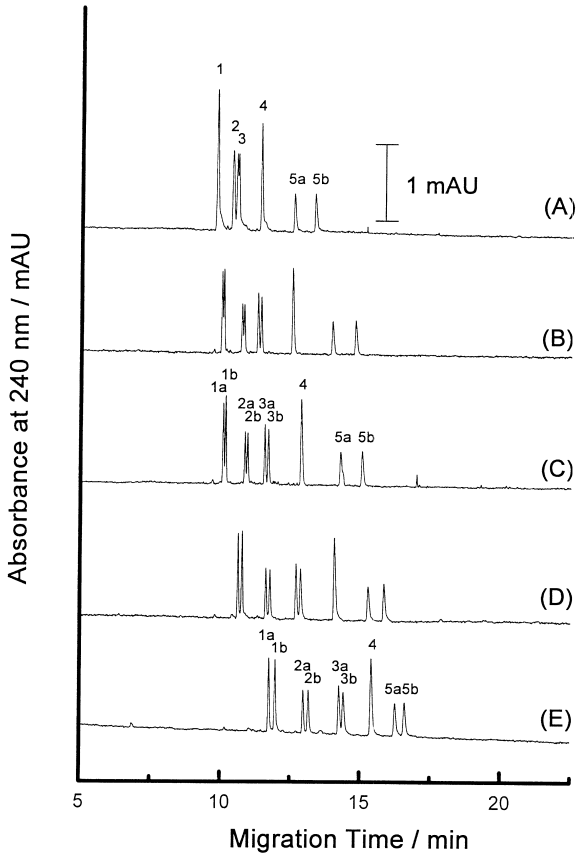


Fig. 5. Electropherograms of phenothiazines obtained with 40 m*M* phosphate buffer containing varied concentrations of γ-CD at pH 3.0: (A) 0.5 m*M*, (B) 1.2 m*M*, (C) 1.6 m*M*, (D) 3.5 m*M*, and (E) 8.0 m*M*. Peak identification as for Fig. 2.

m*M*, respectively. For illustration, Fig. 5A–E show some typical electropherograms of these five phenothiazines with addition of γ-CD at 0.5, 1.2, 1.6, 3.5, and 8.0 m*M*, respectively. With addition of 0.5 m*M* γ-CD, trimeprazine was separated from ethopropazine and the enantiomers of trimeprazine were barely resolved (Fig. 5A). The enantiomers of trimeprazine were baseline separated with addition of 1.6 m*M* γ-CD, whereas the enantiomers of promethazine and ethopropazine were not completely separated (Fig. 5C). It seemed that, unlike the cases of HP-β-CD and β-CD, the enantioselectivity of trimeprazine did not significantly increase with increasing γ-CD concentration from 1.6 to 8.0 m*M* while keeping the two enantiomers baseline separated (Fig. 5E). Beyond 8.0 m*M* of γ-CD, the resolution of the peaks of the two enantiomers of trimeprazine decreased. On the other hand, the peaks of the two enantiomers of promethazine and ethopropazine were barely resolved with 1.2 m*M* γ-CD (Fig. 5B); complete enantioseparation of promethazine and ethopropazine was achieved with 3.5 m*M* γ-CD (Fig. 5D). Similarly, the enantioselectivity of promethazine and ethopropazine increased slightly with increasing γ-CD concentration, reaching its maximum value at about 15.0 m*M*, and then decreased slightly with further increasing the γ-CD concentration from 15.0 to 21.0 m*M*, while keeping the two enantiomers of promethazine and ethopropazine baseline separated [25].

3.5. Effective enantioseparation

The concentration ranges of CDs for effective enantioseparation of the five phenothiazines, together with the observed optimal CD concentration ranges, are summarized in Table 1. As indicated, effective

Table 1
Concentration ranges of CDs for effective enantioseparation of phenothiazines

Peak No.	Phenothiazine	Concentration range for effective enantioseparation[a] (m*M*)		
		HP-β-CD	β-CD	γ-CD
1	Promethazine	–	0.2–3.0 (0.8–1.2)	2.5–21.0 (8.0–12.0)
2	Ethopropazine	0.4–10.0 (1.2–1.6)	–	2.0–12.0 (6.0–10.0)
3	Trimeprazine	0.1–6.0 (0.8–1.2)	0.02–2.0 (0.2–0.3)	1.2–6.0 (4.0–6.0)
4	Methotrimeprazine	–	–	–
5	Thioridazine	0.2–0.3 (<0.2)	0.02–0.3 (<0.05)	0.1–12.0 (0.5–1.2)

[a] The numbers in parentheses are the observed optimal CD concentration ranges.

enantioseparation of promethazine, ethopropazine, trimeprazine, and thioridazine can be simultaneously achieved with γ-CD at a concentration in the range 2.5–6.0 m*M*. On the other hand, simultaneous and effective enantioseparation of promethazine, trimeprazine and thioridazine can be accomplished with β-CD only in a limited concentration range (0.1–0.3 m*M*).

For a better understanding of the enantioseparation of each individual phenothiazine with various CDs, it is of interest to compare the observed and calculated optimal CD concentrations. The optimal CD concentrations ($C_{optimal}$) were calculated based on the equation $C_{optimal} = (K_1K_2)^{-1/2}$, where K_1 and K_2 are the binding constants of the two enantiomers of each individual phenothiazine. The optimal CD concentrations calculated for ethopropazine, trimeprazine and thioridazine with HP-β-CD were 1.4, 0.3 and 0.1 m*M*, respectively; those for promethazine, trimeprazine and thioridazine with β-CD were 0.8, 0.2 and 0.03 m*M*, respectively, and those for promethazine, ethopropazine, trimeprazine and thioridazine were 9.5, 5.8, 2.7 and 0.6 m*M*, respectively. The calculated optimal CD concentrations are in good agreement with the observed values for these phenothiazines, except trimeprazine. The results clearly indicate that effective enantioseparation of phenothiazines occurs more readily with the use of CDs at concentrations less than 6 m*M*. This is particularly true for enantioseparation of trimeprazine and thioridazine with HP-β-CD and enantioseparation of promethazine, trimeprazine and thioridazine with β-CD.

4. Conclusion

Effective enantioseparation of promethazine, ethopropazine, trimeprazine and thioridazine in capillary zone electrophoresis was simultaneously achieved with cyclodextrins (CDs) as a chiral selector using a phosphate buffer at pH 3.0. Because phenothiazines interact strongly with CDs, the use of CDs at relatively low concentrations is sufficient to achieve effective enantioseparation. The results of the present investigation may also suggest that the separation of phenothiazine derivatives is advantageous using CDs as electrolyte modifiers.

Acknowledgements

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