# Chiral Quantitation of Pheniramine, Chlorpheniramine, and Brompheniramine Maleates by Capillary Zone Electrophoresis

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## Abstract

**Cyclodextrin-mediated capillary zone electrophoresis is described for the simultaneous separation and quantitation of chiral pheniramine maleate, chlorpheniramine maleate, and brompheniramine maleate using scopolamine *N*-oxide as an internal standard. The chiral analysis of these drugs is performed in a phosphate buffer (75mM; pH 3.50) with β-cyclodextrin (10mM) and soluble anionic carboxymethyl β-cyclodextrin polymer (4 mg/mL) as chiral selectors. Several parameters affecting the separation are studied, including the type of chiral selector, the concentrations of phosphate buffer and chiral selector, and the pH of the buffer. The linear range of the method for the quantitation of these drugs is 25~150µM for pheniramine maleate, chlorpheniramine maleate, or brompheniramine maleate, each as its enantiomer. This method is successfully applied to the assay of dexchlorpheniramine maleate in tablets.**

## Introduction

Pheniramine maleate (PR), chlorpheniramine maleate (CP), and brompheniramine maleate (BP) are antihistamines of substituted propylamine series. They are highly potent and widely used in very low doses for the treatment of allergies. There is a chiral center in each PR, CP, and BP (Figure 1). The antihistaminic activity reportedly exists predominantly in the dextro-isomer (1,2). Both CP and BP are commercially available as their racemates or dextro-isomers. The assay methods of the Pharmacopeiae (3) for dexchlorpheniramine maleate (d-CP) and dexbrompheniramine maleate (d-BP) in tablet or bulk are relatively non-selective, including non-aqueous titration and ultraviolet (UV) absorption spectrophotometry. These assay methods cannot differentiate the more potent dextro-isomer from the related racemate of CP or BP.

Because of the many advantages of capillary electrophoresis (CE), such as high resolution, low amounts of sample and reagent, fast analysis, and ease of automation, an increasing usage of CE in industrial pharmacy and related fields is not surprising, based on the need for high efficiency, low cost, and less reagent pollution. A number of CE methods have been reported for the chiral analysis of pheniramine-related antihistamines (4–12), mainly for the qualitative analysis of standard samples of PR, CP, or BP. In general, high precision in CE analysis is not as easily attainable as that in HPLC. No reports are available for the quantitative chiral analysis of PR, CP, and BP in drug formulations. In the present work, a simple capillary zone electrophoresis (CZE) method is developed for the simultaneous quantitation of chiral PR, CP, and BP with mixed chiral selectors of β-cyclodextrin (β-CD) and anionic carboxymethyl β-CD polymer (CM-βCD). These reagents are commercially available and relatively inexpensive. Application of the method to the chiral quantitation of d-CP in tablets proves to be satisfactory. The method can be used for the quality control of chiral PR, CP, and BP in bulk and formulations.

## Experimental

### Apparatus and CE conditions

A Beckman P/ACE System 2200 (Fullerton, CA) equipped with a

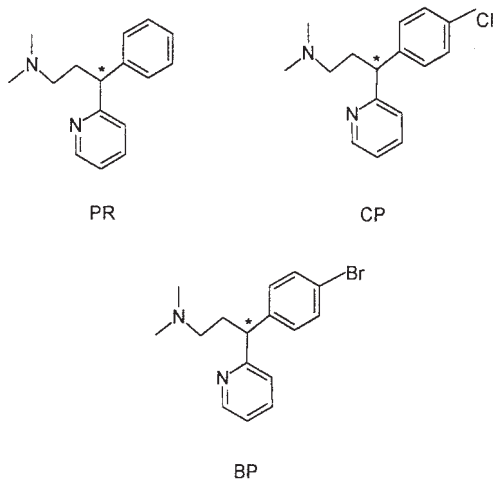


**Figure 1.** Structures of PR, CP, and BP, all shown as free bases.

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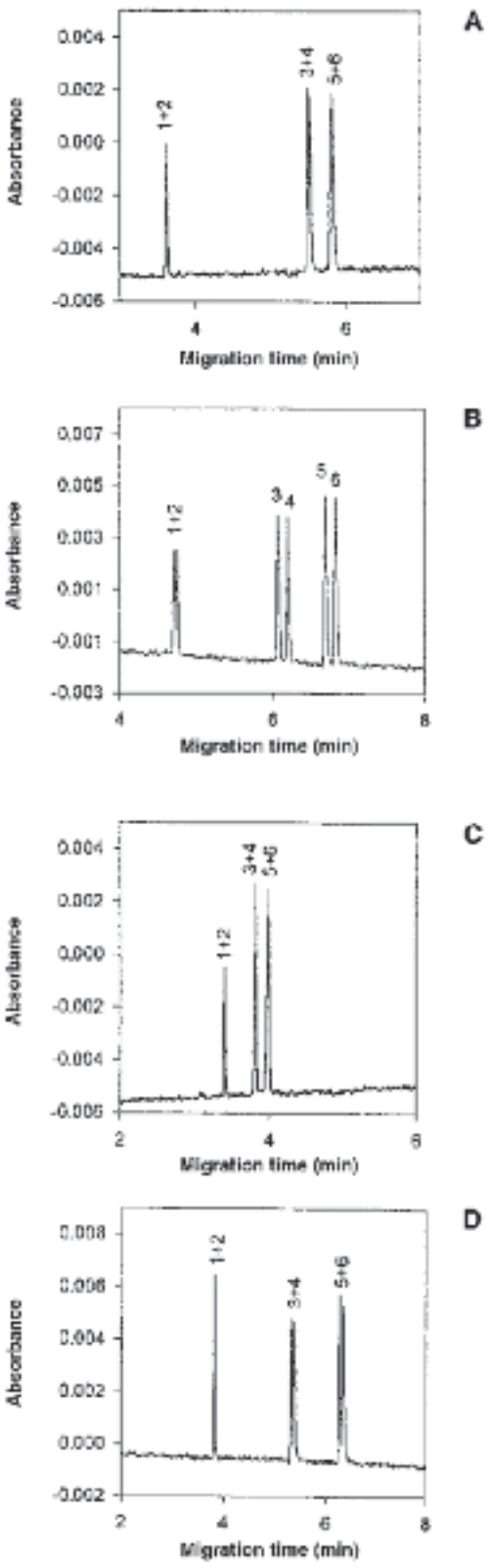


**Figure 2.** Effects of chiral selectors on the resolution of racemic PR (peaks 1 and 2), racemic CP (peaks 3 and 4) and racemic BP (peaks 5 and 6) at 200µM. Electropherograms: 10mM α-CD (A), 10mM β-CD (B), 10mM γ-CD (C), and 10mM dimethyl β-CD (D) in 75mM phosphate buffer (pH 3.50).

UV detector filter and a liquid-cooling device was used. Cyclodextrin (CD)-mediated CZE was performed in an uncoated fused-silica capillary (37 cm × 50-µm i.d., 30-cm effective length, Polymicro, Phoenix, AZ) with a detector (200 nm) at the cathode end. Samples were injected using pressure (0.5 psi) for 2 s, and the applied voltage was 16 kV. Chiral analysis was performed at approximately 25°C in phosphate buffer (75mM; pH 3.50) with a mixture of β-CD (10mM) and CM-β-CD (4 mg/mL). A Beckman Gold software system was used for data processing.

### Chemicals and buffer solutions

PR, CP, BP, scopolamine *N*-oxide (SO), diphenhydramine–HCl, d-CP, and d-BP were from Sigma (St. Louis, MO); α-CD, β-CD, γ-CD, and dimethyl β-CD were from TCI (Tokyo, Japan); CM-β-CD was from Cyclolab (Budapest, Hungary); and sodium hydrogen phosphate ($NaH_2PO_4$–$H_2O$) and phosphoric acid (85%) were from E. Merck (Darmstadt, Germany). All were used without further treatment. d-CP tablets (Yung-Shin, Taichung, Taiwan) and other reagents were of analytical reagent grade. Milli-Q (Millipore, Milford, MA) treated water was used for the preparation of buffer and related aqueous solutions. Solutions of various phosphate buffer at pH 3.50 were prepared by neutralizing the appropriate $NaH_2PO_4$ solution with $H_3PO_4$.

### Reference and sample solutions

Reference solutions of PR, CP, and BP at various concentrations and an internal standard solution of 300µM SO were prepared in water. The sample solution for the d-CP content uniformity test was prepared by dissolving each tablet of d-CP in 0.1M HCl in a 25-mL volumetric flask with the aid of sonification for 5 min. A suitable amount (10 mL) of the resulting water extract was cen-

**Table I. Analytical Results for the Enantiomeric Ratios of Pheniramine-Related Drugs (*n* = 8)**

| Concentration (µM) | Corrected peak-area ratio* |
|---|---|
| **PR** | |
| 140 | 1.004 ± 0.028 |
| 80 | 1.014 ± 0.040 |
| 40 | 1.034 ± 0.028 |
| Mean | 1.017 |
| SD | 0.015 |
| **CP** | |
| 140 | 1.013 ± 0.026 |
| 80 | 1.010 ± 0.033 |
| 40 | 1.004 ± 0.034 |
| Mean | 1.009 |
| SD | 0.005 |
| **BP** | |
| 140 | 1.025 ± 0.025 |
| 80 | 1.020 ± 0.030 |
| 40 | 1.044 ± 0.030 |
| Mean | 1.030 |
| SD | 0.013 |

* Corrected peak-area ratio expressed as (peak area 1/time 1)/(peak area 2/time 2); 1 and 2 correspond to the first migrant and second migrant of each enantiomeric pair, respectively.

trifuged at 280 × *g* for 10 min. The supernatant was filtered, and the filtrate was used for the content uniformity test of d-CP in each tablet. The sample solution for the assay of d-CP was prepared as follows: 20 tablets of d-CP were weighed and finely powdered. An accurately weighed portion of the powder equivalent to approximately 2 mg of d-CP was transferred into a 25-mL volumetric flask with the aid of 0.1M HCl, and then 0.1M HCl was added to the volume. The dissolution of d-CP in 0.1M HCl was effected with sonification for 5 min. A suitable amount (10 mL) of the water extract was centrifuged and filtered as stated previously for the content uniformity test of d-CP. The resulting filtrate was used for the assay of d-CP content in tablets as regulated by various pharmacopeia. Each milliliter of the aforementioned sample solution was mixed with 1.0 mL of internal standard solution for the CD-mediated CZE unless stated otherwise. The final concentrations of PR, CP, BP, and internal standard are expressed as the dilution of the drug sample solution with the internal standard, if any.

## Results and Discussion

Enantioseparation of PR, CP, and BP at 200µM using CZE was briefly studied using common and less expensive chiral selectors (α-CD, β-CD, γ-CD, or dimethyl β-CD, each at 10mM) in phosphate buffer (75mM; pH 3.50) with other CE conditions, as stated in the previous section. The results indicate that no resolution *(R)* was found in the cases using α-CD and γ-CD, but partial resolution for CP ($R$ = 0.88) and BP ($R$ = 0.89) and no resolution for PR was found in cases using dimethyl β-CD. A better resolution is obtainable for CP ($R$ = 1), BP ($R$ = 1) and PR ($R$ = 0.78) using β-CD (Figure 2). Here, the resolution is simply expressed as $R = (hm - hv)/hm$ (13), where *hm* is the mean peak height, and *hv* is the height of the valley. This gives values of $R$ between 0 (no resolution) and 1 (baseline resolution). The results indicate that β-CD-related compounds are potential chiral selectors for the resolution of PR, CP, and BP under present CE conditions. Further study of the enantioseparation of PR, CP, and BP was performed using another β-CD analogue (CM-β-CD, also an inexpensive chiral selector) in the same phosphate buffer. The results indicate that the complete resolution of PR, CP, and BP is attainable, as shown in Figure 3, but the enantiomeric peaks of CP and BP are relatively broad and tailing. Improving peak shapes using organic additives, including acetonitrile, methanol, and isopropanol, is not effective (data not shown). A further investigation was made of the resolution of PR, CP, and BP using the mixed CDs CM-β-CD (2 mg/mL) and β-CD (10mM) in phosphate buffer (75mM; pH 3.50). The results are encouraging (Figure 3); all enantiomeric peaks are sharp and nearly well-resolved. As a consequence, a study focusing on the adjustment of the mixed-CD concentration, buffer pH, and buffer concentration was investigated.

### Concentration of the mixed CD

The effects of various concentrations of β-CD and CM-β-CD in phosphate buffer (75mM; pH 3.50) were studied. Figure 4 shows the separation resulting from a mixed CD of CM-β-CD (0, 2, 4, and 6 mg/mL) with a constant concentration of b-CD (10mM) in the buffer. Baseline resolution of PR, CP, and BP is obtainable using a mixed CD of CM-β-CD (≥ 4 mg/mL) and β-CD (10mM). Figure 5 shows the results from a mixed CD of β-CD (0, 2, 6, 10, and 14mM) with a constant concentration of CM-β-CD (4 mg/mL). A significant peak shape improvement is obtainable by increasing the concentration of β-CD, leading to sharp and well-resolved peaks of PR, CP, and BP enantiomers using a mixture of CM-β-CD (4 mg/mL) and β-CD (≥ 10mM).

The detailed mechanism of added β-CD giving sharper peak shapes than CM-β-CD alone is unknown. The effect of added β-CD on the improvement of the peak shapes of CP or BP enantiomers in the buffer with CM-β-CD could be dynamically multiple (14,15), including at least the competition of β-CD with CM-β-CD in the inclusion of CP or BP enantiomers.

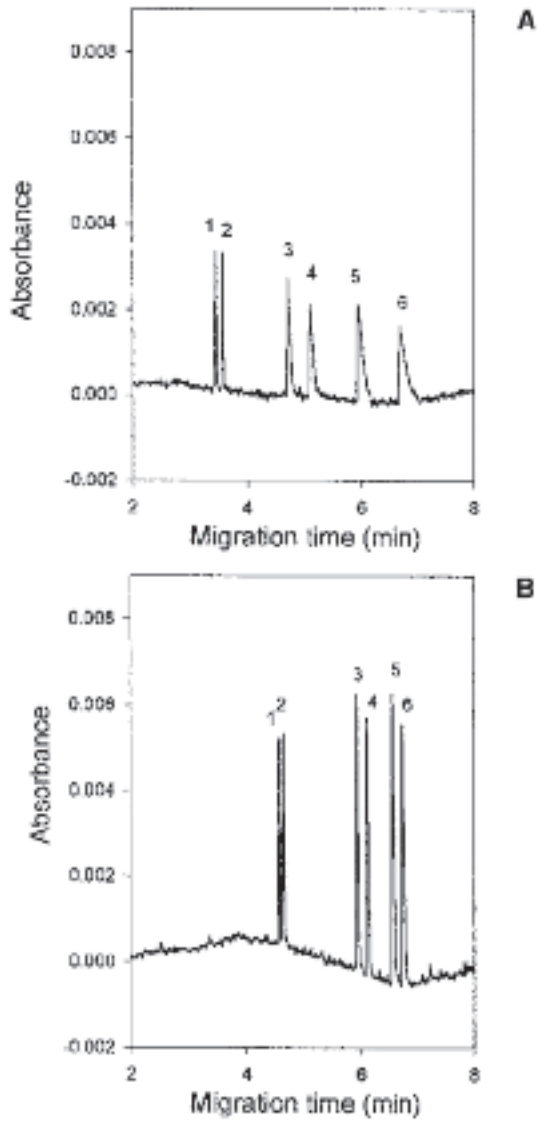


**Figure 3.** Electropherograms for CD-mediated capillary zone electrophoresis of pheniramine-related drugs at 200µM; 4 mg/mL of anionic CM-β-CD (A) and 10mM β-CD plus 2 mg/mL CM-β-CD (B) in 75mM phosphate buffer (pH 3.50).

**Concentration of phosphate buffer**

The effect of various concentrations of phosphate buffer (25, 50, 75, and 100mM at pH 3.50) with the mixture of β-CD (10mM) and CM-β-CD (4 mg/mL) on the separation of PR, CP, and BP enantiomers was studied. Baseline resolution was obtainable at a buffer concentration ≥ 50mM (Figure 6), and the buffer concentration at 75mM was selected for CE.

**pH of buffer**

Free forms of PR, CP, and BP are weak bases and insoluble in neutral water solutions. The effect of the various acidic pH values (2.50, 3.00, 3.50, 4.00, and 4.50) on the separation of PR, CP, and BP in the phosphate buffer with the mixed CDs was studied. The results (Figure 7) indicate that the baseline resolution of PR, CP, and BP enantiomers is attainable at pH 3.50 or 4.00. Incomplete separation occurred using CE at lower pH (2.50 or 3.00), resulting from the suppressed ionization of weak acidic CM-β-CD and increased protonation of the weakly basic nitrogen in the pyridine moiety of each drug (Figure 1), in turn decreasing the chiral separation window, especially for PR. Incomplete separation also occurs at higher pH (4.50), resulting from a stronger electroosmotic flow and giving faster migrations of PR, CP, and BP.

**Identity of enantiomeric peak**

The enantiomeric peaks of PR, CP, and BP from a reference solution of PR, CP, or BP at 200µM in Figure 8 were identified by spiking d-CP or d-BP at 50µM. The results indicate that peaks 3 and 4 are enantiomers of CP, with the lesser migration peak 4 identified as d-CP. Peaks 5 and 6 are from the BP enantiomers, with the lesser migration peak 6 identified as d-BP. No PR enantiomers are available. Therefore, peaks 1 and 2 from PR enantiomers cannot be identified, but from the assignment of CP and BP enantiomers (the lesser migration peaks all belonging to the dextro-enantiomers of CP and BP, which are better fitting to the mixed CD), peaks 1 and 2 from PR enantiomers may be specu-

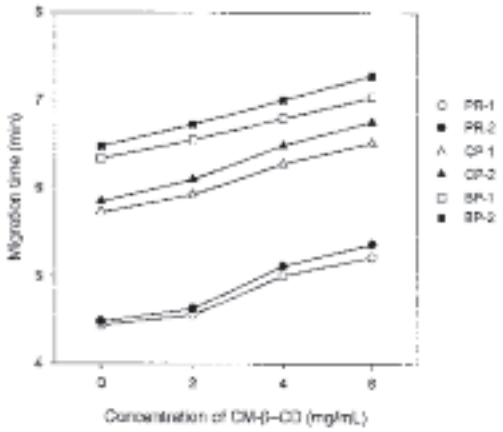


**Figure 4.** Effects of CM-β-CD concentrations on the migration of pheniramine-related drugs in the presence of fixed β-CD (10mM) in phosphate buffer (75mM; pH 3.50). Enantiomeric pairs of PR-1/PR-2, CP-1/CP-2 and BP-1/BP-2 for PR, CP, and BP, respectively, with the first migrant corresponding to 1 and the second migrant correspondeing to 2 for each pair.

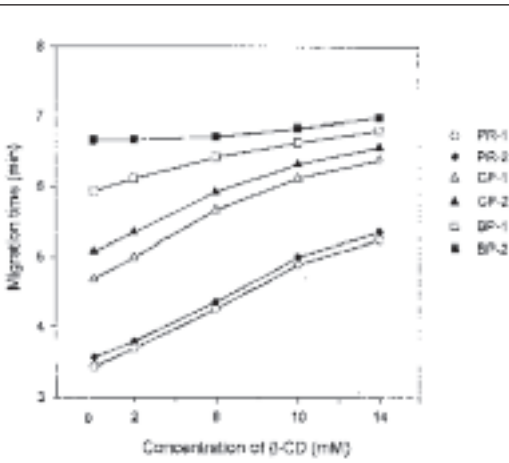


**Figure 5.** Effects of β-CD concentrations on the migration of pheniramine-related drugs in the presence of fixed CM-β-CD (4 mg/mL) in phosphate buffer (75mM; pH 3.50).

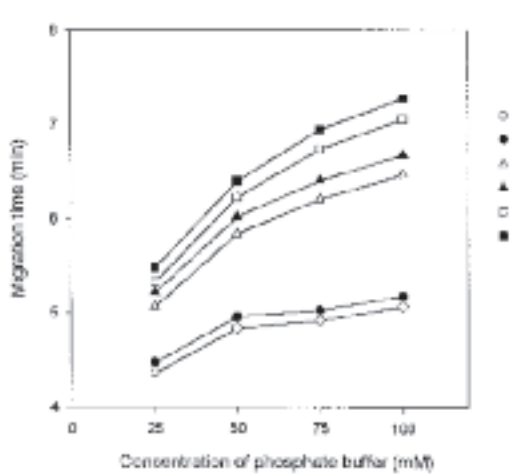


**Figure 6.** Effects of buffer concentration on the migration of pheniramine-related drugs at 200µM in the presence of mixed CDs of 10mM β-CD and 4 mg/mL CM-β-CD in phosphate buffer (pH 3.50).

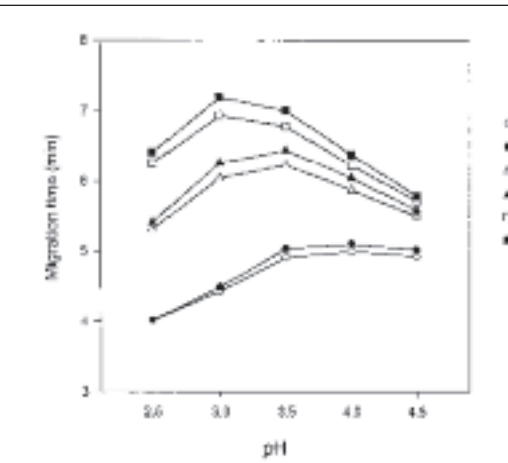


**Figure 7.** Effects of buffer pH on the migration of pheniramine-related drugs in the presence of mixed CDs of 10mM β-CD and 4 mg/mL CM-β-CD in phosphate buffer (75mM).

lated as having the same behavior, with peak 2 corresponding to the dextromer of PR.

**Racemate as enantiomer source**

The higher cost and limited availability of various standard enantiomers always trouble the chiral analyst, especially in the field of industrial pharmacy. The applicability of reference racemates PR, CP, and BP as the source of related enantiomers was investigated. Reference solutions of racemates PR, CP, and BP at various concentrations (280, 160, and 80µM) were prepared. The corrected peak ratios (16) of each enantiomeric pair were calculated (i.e., the ratio of the area of the first migrating enantiomeric peak normalized by its migration time to the ratio of the second migrating enantiomer). The results are shown in

**Table II. Precision and Accuracy for the Determination of PR, CP, and BP**

| | Concentration known (µM) | Concentration found (µM) | RSD* (%) | RE (%) |
|---|---|---|---|---|
| *Intraday analysis* (n = *5*) | | | | |
| PR-1 | 40 | 41.36 ± 1.60 | 3.87 | +3.40 |
| | 80 | 81.04 ± 2.75 | 3.39 | +1.30 |
| | 140 | 139.41 ± 2.64 | 1.89 | –0.42 |
| PR-2 | 40 | 40.28 ± 1.76 | 4.37 | +0.70 |
| | 80 | 80.40 ± 1.82 | 2.26 | +0.50 |
| | 140 | 139.06 ± 3.78 | 2.72 | –0.67 |
| CP-1 | 40 | 39.02 ± 0.94 | 2.41 | –2.45 |
| | 80 | 79.84 ± 2.17 | 2.72 | –0.20 |
| | 140 | 142.18 ± 3.41 | 2.40 | +1.56 |
| CP-2 | 40 | 39.42 ± 1.29 | 3.27 | –1.45 |
| | 80 | 79.14 ± 1.43 | 1.81 | –1.07 |
| | 140 | 139.51 ± 3.78 | 2.71 | –0.35 |
| BP-1 | 40 | 40.13 ± 1.16 | 2.89 | +0.32 |
| | 80 | 81.13 ± 1.61 | 1.98 | +1.41 |
| | 140 | 143.18 ± 3.02 | 2.11 | +2.27 |
| BP-2 | 40 | 40.28 ± 0.93 | 2.31 | +0.70 |
| | 80 | 81.48 ± 0.76 | 0.93 | +1.85 |
| | 140 | 142.59 ± 2.02 | 1.42 | +1.85 |
| *Interday analysis* (n = *5*) | | | | |
| PR-1 | 40 | 39.39 ± 1.76 | 4.47 | –1.52 |
| | 80 | 80.55 ± 0.99 | 1.23 | +0.69 |
| | 140 | 142.04 ± 2.70 | 1.90 | +1.46 |
| PR-2 | 40 | 40.22 ± 1.18 | 2.93 | +0.55 |
| | 80 | 80.89 ± 1.65 | 2.04 | +1.11 |
| | 140 | 140.69 ± 1.86 | 1.32 | +0.49 |
| CP-1 | 40 | 39.88 ± 1.45 | 3.63 | –0.30 |
| | 80 | 79.91 ± 1.48 | 1.85 | –0.11 |
| | 140 | 141.08 ± 0.93 | 0.66 | +0.77 |
| CP-2 | 40 | 40.15 ± 1.30 | 3.24 | +0.37 |
| | 80 | 79.87 ± 1.58 | 1.98 | –0.16 |
| | 140 | 140.54 ± 2.98 | 2.12 | +0.38 |
| BP-1 | 40 | 39.74 ± 1.40 | 3.52 | –0.65 |
| | 80 | 79.98 ± 1.97 | 2.46 | –0.03 |
| | 140 | 142.38 ± 2.28 | 1.60 | +1.70 |
| BP-2 | 40 | 39.90 ± 1.22 | 3.06 | –0.25 |
| | 80 | 79.67 ± 1.62 | 2.03 | –0.41 |
| | 140 | 140.94 ± 3.14 | 2.23 | +0.67 |

* RSD, relative standard deviation; RE, relative error.

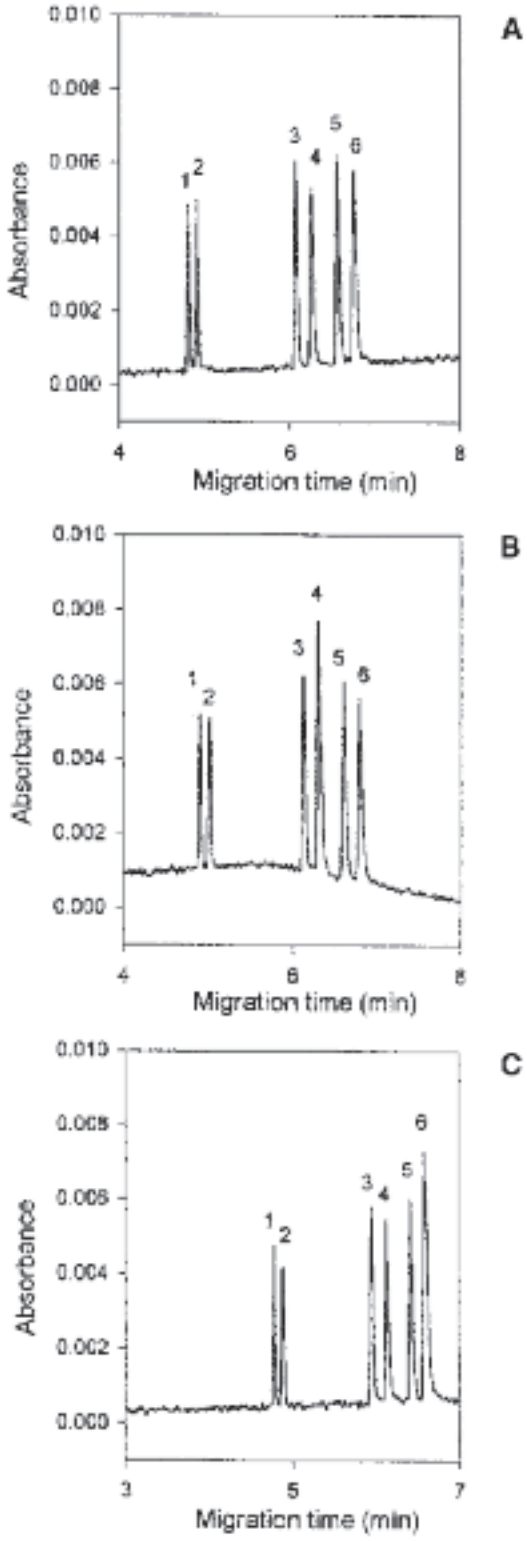


**Figure 8.** Electropherograms from the identities of enantiomeric peaks of pheniramine-related drugs: a standard mixture of PR (peaks 1 and 2), CP (peaks 3 and 4) and BP (peaks 5 and 6) (A); the same standard mixture spiked with 50µM d-CP (B); and the standard mixture spiked with 50µM d-BP (C), clearly showing that peaks 4 and 6 are related to d-CP and d-BP, respectively.

**Table III. Analytical Results for Content Uniformity of d-CP in Tablets Obtained from a Commercial Source**

| Sample* | Amount found (mg) | Percentage of claimed content (%) | |
|---|---|---|---|
| 1 | 2.11 ± 0.02 | 105.5 | |
| 2 | 2.05 ± 0.05 | 102.5 | |
| 3 | 2.07 ± 0.01 | 103.5 | |
| 4 | 2.06 ± 0.01 | 103.0 | |
| 5 | 2.06 ± 0.04 | 103.0 | |
| 6 | 2.06 ± 0.05 | 103.0 | |
| 7 | 2.02 ± 0.03 | 101.0 | |
| 8 | 2.10 ± 0.02 | 105.0 | |
| 9 | 2.06 ± 0.05 | 103.0 | |
| 10 | 2.08 ± 0.05 | | 104.0 |

* The labeled amount of d-CP in each tablet is 2 mg.
† Mean ± SD of triplicate analyses.
‡ Content uniformity test is used to check the variation of dexchlorpheniramine maleate in each tablet.

**Table IV. Assay Results of d-CP in Tablets Obtained from a Commercial Source**

| Sample* | Amount found (mg) | Percentage of claimed content (%) | |
|---|---|---|---|
| 1 | 2.02 ± 0.04 | 101.0 | |
| 2 | 2.04 ± 0.06 | 102.0 | |
| 3 | 2.05 ± 0.03 | 102.5 | |
| Mean | | | 101.8 |
| SD | | 0.8 | |

* Labeled amount of dexchlorpheniramine maleate in each tablet is 2 mg.
† Mean ± SD of five replicate analyses.

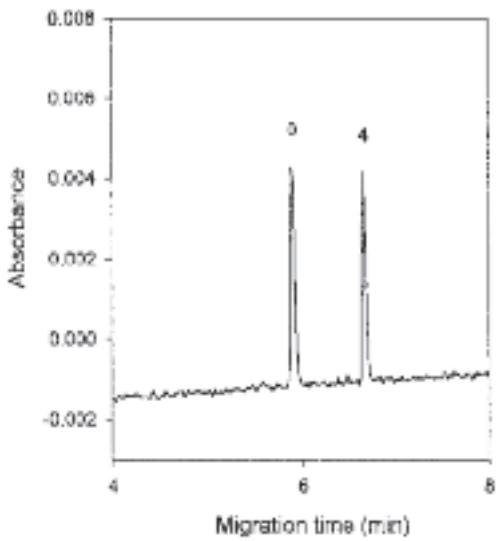


**Figure 9.** Typical electropherogram for the analysis of d-CP in tablets. Peaks 0 and 4 correspond to SO (internal standard) and d-CP, respectively.

Table I. The mean enantiomeric ratios of PR, CP, and BP are 1.017 ± 0.015, 1.009 ± 0.005, and 1.030 ± 0.013, respectively, indicating that the enantiomeric ratio of each racemate is approximately unity, equivalent to a 50:50 mixture of the enantiomers based on the method used. Therefore, the commercial racemates of PR, CP, and BP are used as the sources of their related enantiomers for calibration.

### Analytical calibration

For evaluating the quantitative applicability of the method, 5 different concentrations of PR-1, PR-2, CP-1, CP-2, BP-1, and BP-2 for the enantiomeric pairs of PR, CP, and BP in the range of 25~150µM were analyzed using SO as an internal standard. The internal standard is stable under the present CE conditions for 24 h; no significant changes in corrected peak-area ratio of the internal standard to diphenhydramine–HCl were observed. PR-1, CP-1, and BP-1 stand for the first migration enantiomer of each enantiomer pair versus their second migrating counterparts PR-2, CP-2, and BP-2, respectively. The linearity between the corrected peak-area ratio ($y$) of an analyte to the internal standard and the concentration ($x$, µM) of the analyte was studied. The linear regression equations ($n$ = 3) obtained were as follows: $y$ = (0.0089 ± 0.0035) + (0.00562 ± 0.00013)$x$ (correlation coefficient $r$ = 0.998) for PR-1, $y$ = (0.0029 ± 0.0073) + (0.00565 ± 0.00006)$x$ ($r$ = 0.999) for PR-2, $y$ = (0.0132 ± 0.0118) + (0.00764 ± 0.00015)$x$ ($r$ = 0.999) for CP-1, $y$ = (0.0102 ± 0.0219) + (0.00761 ± 0.00029)$x$ ($r$ = 0.999) for CP-2, $y$ = (0.0089 ± 0.0102) + (0.00811 ± 0.00011)$x$ ($r$ = 0.999) for BP-1, and $y$ = (–0.0004 ± 0.0065) + (0.00803 ± 0.00009)$x$ ($r$ = 0.999) for BP-2.

The results indicate that a high linearity between y and x is attainable over the range studied. The lower detection limits of PR-1, PR-2, CP-1, d-CP, BP-1, and d-BP are all approximately 6µM, based on a signal-to-noise ratio of 3. The relative standard deviations (RSDs) of the method based on the concentration levels of 40, 80, and 140µM of each enantiomer are shown in Table II. The results indicate that the intraday RSDs (n = 5) are all below 4.4%, with better RSDs (≤ 2.8%) at high test levels; similarly, the interday RSDs ($n$ = 5) are all below 4.5% with better RSDs (≤ 2.3%) at high test levels.

### Application

Application of the method to the analysis of d-CP in tablets (2 mg per tablet) was studied, including the uniformity test (a test to evaluate the content variation of d-CP in each tablet) and the assay (an analysis for evaluating the average content of d-CP in 20 tablets) usually required by an official pharmacopeia for quality control of the tablet formulation. The sample solutions of d-CP (in the Reference and sample solutions section) were used for the study of content uniformity and the assay. The results are given in Tables III and IV. The analytical values from 10 tablets (Table III) fall within the labeled amount of 85.0~115.0% required by the United States Pharmacopeia (USP), and those analytical results of the assay (Table IV) also pass the USP requirement based on the content range 90.0~110.0% of the labeled amount.

The solvents used for the extraction and preparation of d-CP solution from pulverized tablet were tested with water and 0.1M HCl. The results ($n$ = 5) indicate that the recoveries from water

and acidic water (0.1M HCl) extraction are 90.1 ± 2.7% and 101.2 ± 1.8% of the labeled amount of d-CP, respectively. The acidic water is better for the extraction of the basic drug (d-CP) and was selected for the extraction of d-CP in tablet. A recovery test for d-CP stated elsewhere gives the quantitative yield using 0.1M HCl for the extraction of d-CP in tablets.

A typical electropherogram for the analysis of d-CP in tablet is shown in Figure 9. The recoveries of d-CP were studied by simply spiking known amounts of reference racemate CP as the source of d-CP (calculated as half the amount of each enantiomer) to the pulverized tablets of d-CP, resulting in the preparation of 4 spiked levels of d-CP (0, 30, 50, and 100µM) for analysis. The tablet powder with 0µM d-CP was used for the analysis of d-CP content in the initial powder with no spiking as a control value for recovery calculation. All the recoveries are above 98% with a range of 98.9~101.6%.

## Conclusion

In conclusion, simple CD-mediated CZE has been established for the quantitation of chiral antihistamines PR, CP, and BP. Application of the method to the analysis of chiral d-CP in tablets proves satisfactory. The method could be used for the quality control of PR, CP, and BP in bulk and drug formulation.

## Acknowledgments

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## References

1. J.N. Delgads and W.A. Remers. *Wilson and Gisvald's Textbook of Organic Medical and Pharmaceutical Chemistry,* 9th ed. J.B. Lippincott, Philadelphia, PA, 1991, pp 611–12.
2. A.R. Gennaro. *Remington: The Science and Practice of Pharmacy,* 19th ed. Mack Publishing, Easten, PA, 1995, p 1225.
3. USP 23/NF 18. United States Pharmacopeial Convention, Rockville, MD, 1995, pp 476–77.
4. H. Nishi and S. Terabe. Application of micellar electrokinetic chromatography to pharmaceutical analysis. *Electrophoresis* **11:** 691–701 (1990).
5. K. Otsuka and S. Terabe. Optical resolution of chlorpheniramine by cyclodextrin added capillary zone electrophoresis and cyclodextrin modified micellar electrokinetic chromatography. *J. Liq. Chromatogr.* **16:** 945–53 (1993).
6. A.M. Stalcup and N.M. Agyei. Heparin: a chiral mobile-phase additive for capillary zone electrophoresis. *Anal. Chem.* **66:** 3054–59 (1994).
7. S. Palmarsdottir and L.E. Edholm. Capillary zone electrophoresis for separation of drug enantiomers using cyclodextrins as chiral selectors. *J. Chromatogr. A* **666:** 337–50 (1994).
8. I. Bechet, P. Paques, M. Fillet, P. Hubert, and J. Crommen. Chiral separation of basic drugs by capillary zone electrophoresis with cyclodextrin additives. *Electrophoresis* **15:** 818–23 (1994).
9. C. Quang and M.G. Khaledi. Extending the scope of chiral separation of basic compounds by cyclodextrin-mediated capillary zone electrophoresis. *J. Chromatogr. A* **692:** 253–65 (1995).
10. H. Nishi, K. Nakamura, H. Nakai, and T. Sato. Enantiomeric separation of drugs by mucopolysaccharide-mediated electrokinetic chromatography. *Anal. Chem.* **67:** 2334–41 (1995).
11. B. Koppenhoefer, U. Epperlein, B. Christian, B. Lin, Y. Ji, and Y. Chen. Separation of enantiomers of drugs by capillary electrophoresis III. *J. Chromatogr. A* **735:** 333–43 (1996).
12. S. Fanali. Identification of chiral drug isomers by capillary electrophoresis. *J. Chromatogr. A* **735:** 77–121 (1996).
13. M.Z. El Fallsh and M. Martin. Influence of the peak height distribution on the separation performances: discrimination factor and effect peak capacity. *Chromatographia* **24:** 115–22 (1987).
14. T. Schmitt and H. Engelhardt. Charged and uncharged cyclodextrins as chiral selectors in capillary electrophoresis. *Chromatographia* **37:** 475–81 (1993).
15. L.A. St. Pierre and K.B. Sentell. Cyclodextrins as enantioselective mobile phase modifiers for chiral capillary electrophoresis. Effect of pH and cyclodextrin concentration. *J. Chromatogr. B* **657:** 291–300 (1994).
16. K.D. Altria, D.M. Goodall, and M.S. Rogan. Quantitative applications and validation of the resolution of enantiomers by capillary electrophoresis. *Electrophoresis* **15:** 824–27 (1994).

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