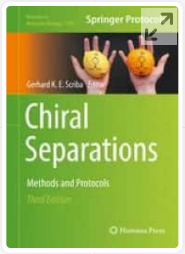

Book | © 2019

Chiral Separations

Methods and Protocols

Editors: Gerhard K. E. Scriba

Includes cutting-edge techniques

Provides step-by-step detail essential for reproducible results

Contains key implementation advice from the experts

Part of the book series: Methods in Molecular Biology (MIMB, volume 1985)

Sections

Editors and Affiliations
Bibliographic Information

Table of contents (27 protocols)

Search within book

← Previous Page 2 of 2 Next →

← Previous Page 2 of 2 Next →

Back to top ↑

About this book

This detailed book focuses on analytical separations by chromatographic and electrophoretic techniques, providing some overview along with numerous practically-oriented applications of the most important analytical techniques in chiral separation sciences. While some compounds may only be enantioseparated with one technique based on the physico-chemical properties, often the analyst can choose between two or more analytical techniques for a given analyte, which requires knowledge of the strengths and weaknesses of each technique in order to select the most appropriate method for the given problem. This collection binds that knowledge in one volume. Written for the highly successful *Methods in Molecular Biology* series, chapters include introductions to their respective topics, lists of the necessary materials and reagents, step-by-step, readily reproducible laboratory protocols, and tips on troubleshooting and avoiding known pitfalls.

Authoritative and practical, *Chiral Separations: Methods and Protocols, Third Edition* serves as a helpful guide for analytical chemists working on stereochemical problems in the fields of pharmacy, chemistry, biochemistry, food chemistry, molecular biology, forensics, environmental sciences, or cosmetics in academia, government, or industry.

Back to top ↑

Keywords

Liquid Chromatography

Electrophoretic techniques

Enantioseparations **Chiral compounds**

Enantiomers **Analytical separations**

Back to top ↑

Reviews

"The book is aimed at investigators in any discipline working in the field of chirality. It will be of special interest to anyone who has a need to separate chiral molecules. ... Detailed protocols are provided for the systems covered in the book that will make it easier for investigators wishing to replicate one of these procedures." (Thomas J. Wenzel, Analytical and Bioanalytical Chemistry, Vol. 411, 2019)

Back to top ↑

Editors and Affiliations

Department of Pharmaceutical Chemistry, University of Jena, Jena, Germany
Gerhard K. E. Scriba

Back to top ↑

Bibliographic Information

Book Title
Chiral Separations

Book Subtitle
Methods and Protocols

Editors
Gerhard K. E. Scriba

Series Title
Methods in Molecular Biology

DOI
https://doi.org/10.1007/978-1-4939-9438-0

Publisher
Humana New York, NY

eBook Packages
Springer Protocols

Copyright Information
Springer Science+Business Media, LLC, part of Springer Nature 2019

Hardcover ISBN
978-1-4939-9437-3
Published: 08 May 2019

eBook ISBN
978-1-4939-9438-0
Published: 08 May 2019

Series ISSN
1064-3745

Series E-ISSN
1940-6029

Edition Number
3

Number of Pages
XIV, 487

Number of Illustrations
91 b/w illustrations, 56 illustrations in colour

Topics
Pharmaceutics, Analytical Chemistry, Biochemistry

Back to top ↑

Chapter 24

Enantioseparation of Selected Imidazole Drugs Using Dual Cyclodextrin-Modified Micellar Electrokinetic Chromatography

Wan Aini Wan Ibrahim, Siti Munirah Abd Wahib, Dadan Hermawan, and Mohd Marsin Sanagi

Abstract

Particular attention has been paid to capillary electrophoresis as versatile and environmentally friendly approach for enantioseparations of a wide spectrum of compounds. Cyclodextrin-modified micellar electrokinetic chromatography (CD-MEKC) is a method of choice to provide effective separation toward hydrophobic and uncharged stereoisomers. The chiral discrimination of the solutes relies upon the partitioning between a given CD in the aqueous phase and micelles formed from a surfactant. Synergistic combinations of chiral selectors, surfactant, and modifier contribute to successful enantioseparations of the enantiomers. In this chapter, an application of CD-MEKC for the enantioseparation of selected imidazole drugs employing a dual CDs system is described.

Key words Enantioseparation, Cyclodextrin-modified micellar electrokinetic chromatography, Imidazole drugs, Dual cyclodextrin

1 Introduction

Capillary electrophoresis (CE) has been highlighted as a prominent tool for the direct separation of chiral compounds. CE offers inherent advantages of high separation power, high flexibility, "green" in terms of less organic solvents and sample consumption, and cost-effective where a small amount of chiral selector is introduced and easily varied in the background electrolyte (BGE). The substances or additives used will differentiate the modes of CE. Capillary zone electrophoresis (CZE) is the simplest way of separation which requires a buffer system at a certain pH to separate analytes based on charge-to-mass ratio. Regarding the principle, CZE cannot resolve chiral compounds since enantiomers are equal in charge density. The common strategy for the separation of chiral compounds is the addition of chiral selectors into the BGE, a technique

Gerhard K. E. Scriba (ed.), *Chiral Separations: Methods and Protocols*, Methods in Molecular Biology, vol. 1985,
https://doi.org/10.1007/978-1-4939-9438-0_24,

known as electrokinetic chromatography (EKC). The concept of chiral recognition is the formation of transient diastereomeric complexes between the stereoisomers and a chiral selector. By far, cyclodextrins (CDs) are the most frequently used chiral selectors for CE enantioseparation. CDs exhibit remarkable properties such as low UV absorbance, inert, stereoselective, water-soluble, and available at a relatively low price as compared to other selectors. CDs are cyclic oligosaccharides with a shape of a truncated cone, having hydrophobic open cavity and hydrophilic outside. The merits of having great shape, flexible structure, possession of a large number of chiral centers, and accessible to substitution make CDs an indisputably preferable selector for countless compounds [1–3].

Native CDs or CD derivatives display different power of discrimination depending on their physicochemical properties. In fact, the suitability of analyte with the cavity size of a CD plays a role in chiral discrimination. Huang et al. [4] suggested that the small cavity of α-CD is recommended for monocyclic aromatic hydrocarbon while β-CD is compatible for the size of naphthalene ring. The cavity of γ-CD is suitable for larger compounds such as analytes with three aromatic rings. The predominant interaction between CDs and analytes is inclusion-complexation with a 1:1 stoichiometry. The degree of enantiorecognition can be determined by the difference in energies of the inclusion complexes between the enantiomers and CD. Enantiorecognition is also driven by the interaction with side chains or substituent groups where hydrogen-bonding, dipole–dipole interaction, steric forces, or π–π interactions may influence the binding between each enantiomer and the CD [5].

In 1984, Terabe et al. [6] developed another mode of CE as an extension of EKC by introducing micellar environment in the BGE. Micellar electrokinetic chromatography (MEKC) often utilizes an anionic surfactant such as sodium dodecyl sulfate (SDS) in the BGE. Theoretically, the anionic micelles (negatively charged) migrate electrostatically toward the anode. However, when the running electrolyte is neutral or under alkaline conditions, the electroosmotic flow (EOF) is stronger and the prevalent velocity of the EOF affects the anionic micelles to migrate toward cathode at a retarded velocity. The micelles form a dynamic equilibrium between single molecules and serve as a pseudostationary phase to solubilize the solute [7]. The separation mechanism of MEKC combines both electrophoretic and a chromatographic effect. The electrophoretic effect is related to mobility difference of solutes while the partition of solutes between micelles and continuous phase which is known as chromatographic effect relies upon the retention difference of the solutes [8]. To make enantioseparations possible, MEKC using chiral surfactants such as bile salts or combination of CD and surfactant can be demonstrated.

Introducing a CD in a MEKC system has been well accepted as an effective technique for enantioseparations of neutral (uncharged) compounds. The basic principle of discrimination is partitioning of the neutral solutes between the aqueous CD phases and the micellar phase. This approach is also feasible for charged compounds, where enantiorecognition is determined by distribution of solute in micellar and aqueous CD phases as well as the differences in electrophoretic mobility [9]. Neutral CDs can be employed in MEKC to resolve neutral compounds as the CD migrates at the same velocity as the EOF and provides chiral recognition for the enantiomer in the presence of an anionic surfactant. Incorporation of a solute in the micelles depends on the hydrophobicity of the solute. For solutes with a high affinity toward the micelles, the reversed polarity mode (anodic detection) to suppress the EOF can be performed to avoid long migration times. Even though SDS is an achiral surfactant, the micelles could influence the nature of CD-solute interaction since the surfactant consists of hydrophobic tail which allows incorporation in the CD cavity along with the solute [10].

If a single CD is insufficient to give satisfactory separation of the enantiomers, dual chiral systems should be considered. Employing two CDs can provide different complexation mechanisms leading to better enantioselectivity toward the chiral solutes. In this regard a complete discrimination of two stereoisomers of miconazole in MEKC mode was accomplished in the presence of β-CD and mono-3-O-phenylcarbamoyl-β-CD [11]. Česla and co-workers [12] developed reversed flow-MEKC consisting of β-CD and *heptakis*(6-O-sulfo)-β-CD as selectors to resolve chiral anacardic acids. The use of neutral and charged CDs contributes to opposite complex affinities and mobilities of the enantiomers in the MEKC system. The simultaneous enantioseparation of cyproconazole, bromuconazole, and diniconazole could not be achieved using a single CD. However, a dual CDs system of HP-β-CD and HP-γ-CD rendered competitive complexation to allow successful enantiorecognition for all analytes [13].

The migration behavior of the enantiomers typically relies upon the affinity toward a given CD, but differences in mobilities are another aspect that should be taken into account [14]. Selector concentration influences the affinity of CD-solute as well as the electrophoretic mobilities of the complexes of the solutes. At low CD concentrations, most of the solute is unbound. Therefore, the migration behavior of stereoisomers is primarily influenced by the stability of the complexes. Increasing selector concentration gives more interaction between CD and analyte to form complexes until it reaches the maximum value, which depends on the binding affinity of CD-solute. When the selector concentration is higher than an optimum value, the migration behavior is profoundly affected by the differences in mobilities of the complexes

[1, 3]. In a MEKC system, selection of the surfactant concentration is usually above its critical micelle concentration (CMC). Higher concentration of the surfactant promotes the enhancement in fraction of the solute partitioning into the CDs micellar phase and improves the resolution of the solutes. Using a very low concentration of surfactant can reduce the efficiency of MEKC, which can be adequately explained by slow mass transfer caused by large distance between micelles and stereoisomers [15]. However, in certain cases, the addition of a surfactant below or close to its CMC benefits an enantioseparation. For example, it was reported that the enantioseparation of the four ketoconazole stereoisomers could be achieved by the addition of only 5 mM SDS in the BGE consisting of 10 mM phosphate buffer (pH 2.5), 20 mM TM-β-CD, and 1.0% methanol [16]. In this scenario, the addition of the surfactant is below the CMC value for SDS (8.0 mM). At this concentration level, the surfactant probably might not serve as a typical pseudostationary phase but could aid in the solubilization of the analyte due to the formation of premicellar system [17] and form effective ion-pair interactions with the ketoconazole enantiomers. Additionally, organic modifiers are also useful candidates that are often introduced in BGE to manipulate enantiomer resolution and selectivity. The incorporation of solvent-micelles disrupts the strong affinity of hydrophobic solutes for the micellar phase, reduces the EOF, and shifts the retention factor of the solutes. The addition of organic modifiers may affect the solubility of enantiomers and chiral selectors and alter the complexation formation as well as the electrophoretic mobilities [10, 18]. The addition of solvents as BGE modifier typically does not exceed 20% (v/v) as higher concentrations of organic modifiers can prolong the migration time and sometimes may deteriorate the micelle aggregates in MEKC.

CD-MEKC is a promising electromigration approach to discriminate a variety of chiral compounds. In Table 1, several successful separations of chiral compounds using CD-modified MEKC based on the articles published from 2010 onwards have been compiled. From the table, neutral CDs or charged CDs were successfully employed in MEKC systems depending on the molecular properties of the solutes as well as synergic combination of the separation buffer. It is also noticeable that neutral CDs were extensively used in CD-MEKC enantioseparations.

In the present chapter, the chiral discrimination of three selected imidazole drugs, namely tioconazole, isoconazole, and fenticonazole, using CD-MEKC is described. The separation employing a dual CD system composed of hydroxypropyl-γ-cyclodextrin (HP-γ-CD) and *heptakis*(2,6-di-*O*-methyl)-β-cyclodextrin (DM-β-CD) in MEKC system is attributed to different inclusion-complexation patterns to consequently improve the enantioselectivity and enantioresolution of the enantiomers [29].

Table 1
Examples of enantioseparations by CD-MEKC dating from 2010 to 2017

Analytes	Chiral selector	Separation buffer	LOD	Ref.
Bioallethrin	Acetyl-β-CD	100 mM borate buffer (pH 8.0), 75 mM sodium deoxycholate, 15 mM acetyl-β-CD, 2 M urea, 30 kV, 25 °C	(*R*)-bioallethrin: 0.2 mg/L (*S*)-bioallethrin: 0.3 mg/L	[19]
Hydroxyeicosatetraenoic acids	HP-γ-CD	30 mM phosphate-5 mM borate buffer (pH 9.0), 75 mM SDS, 30 mM HP-γ-CD, +30 kV, 15 °C, 235 nm		[20]
Ambrisentan and its chiral impurity	γ-CD	100 mM borate buffer (pH 9.2), 100 mM SDS, 50 mM γ-CD, 30 kV, 22 °C		[21]
Methamphetamine (MA)	HS-γ-CD	100 mM phosphate buffer (pH 2.7), 20 SDS, 20% HS-γ-CD, 20% methanol, −18 kV, 25 °C, 195 nm	(*S*)-MA: 77.9 pg/mL (*R*)-MA: 88.8 pg/mL	[22]
Amino acids	β-CD	150 mM Tris-borate (pH 8.5), 35 mM sodium taurodeoxycholate, 35 mM β-CD, 12.5% (v/v) isopropanol, 0.5% (w/v) poly(ethylene oxide)	40–60 nM	[23]
Ketoprofen	S-β-CD TM-β-CD	50 mM borate/NaOH (pH 2.5), 20 mM SDS, 4.0% w/v S-β-CD, 0.5% w/v TM-β-CD	2.5 and 3.4 nM	[24]
Isoquinoline derivative	β-CD	35 mM phosphate buffer saline (pH 7.85), 30 mM sodium deoxycholate, 20 mM β-CD, 20% (v/v) acetonitrile, 20 kV	0.2 and 0.5 μM	[25]
Vinpocetine	HP-β-CD	50 mM phosphate buffer (pH 7.0), 40 mM SDS, 40 mM HP-β-CD 25 °C, 25 kV		[26]
Econazole	HP-γ-CD	20 mM phosphate buffer (pH 8.0), 50 mM SDS, 40 mM HP-γ-CD	3.6 and 4.3 mg/L	[27]
Hexaconazole, penconazole, myclobutanil	HP-γ-CD	25 mM phosphate buffer (pH 3.0), 50 mM SDS, 40 mM HP-γ-CD	1.2–4.0 mg/L	[28]
cis-Bifenthrin	TM-β-CD	100 mM borate buffer (pH 8.0), 100 mM sodium cholate, 20 mM TM-β-CD 2 M urea, 30 kV, 15 °C	4.8 and 3.9 mg/L	[17]

HS-γ-CD highly sulfated-γ-CD
S-β-CD sulfated-β-CD
TM-β-CD heptakis(2,3,6-tri-*O*-methyl)-β-CD

2 Materials

2.1 Instrumentation and Materials

1. A commercial CE instrument such as an Agilent HP^{3D} system (Agilent Technologies, Waldbronn, Germany) or a Beckman P/ACE MDQCE system (Beckman, Fullerton, CA, USA) equipped with a UV or a photo-diode array detector and a temperature control unit.
2. Uncoated fused-silica capillaries with an inner diameter of 50 or 75 μm and an outer diameter of 375 μm. For the experiments described below use a 50 μm capillary with an effective length of 56 cm and a total length of 64.5 cm.
3. A pH-meter for pH adjustment of the background electrolytes.
4. 0.22 or 0.45 μm membrane filters for filtering the background electrolyte and sample solutions.
5. A commercial ultrasonic bath for sonication purpose.

2.2 Background Electrolyte and Sample Solutions

Use ultrapure water obtained from a suitable water purification system or double distilled water. Organic solvents should be of HPLC grade and all chemicals should be of analytical grade.

1. *Phosphate buffer pH 7.0 stock solution (500 mM):* Weigh 4.477 g Na_2HPO_4 12 H_2O in a beaker and dissolve in approx. 20 mL ultrapure water. Adjust to pH 7.0 by addition of 85% phosphoric acid. After pH adjustment, transfer the solution to a 25 mL volumetric flask and dilute to the mark with ultrapure water (*see* **Note 1**).
2. *SDS stock solution (500 mM)*: Weigh 1.44 g SDS in a beaker and add about 5 mL ultrapure water. After dissolution, quantitatively transfer the solution into a 10 mL volumetric flask and dilute to the mark after the bubbles have disappeared.
3. *HP-γ-CD stock solution (100 mM)*: Weigh 0.790 g HP-γ-CD and dissolve the CD in approx. 3 mL ultrapure water. Quantitatively transfer the solution into a 5 mL volumetric flask and add up to final volume with ultrapure water.
4. *DM-β-CD stock solution (100 mM)*: Weigh 0.670 g DM-β-CD and dissolve the selector in about 3 mL ultrapure water. Quantitatively transfer the solution into a 5 mL volumetric flask and dilute to the mark with ultrapure water.
5. *CD-MEKC background electrolyte*: For simultaneous enantioseparation of the three imidazole drugs, run buffer consists of 35 mM phosphate buffer (pH 7), 35 mM HP-γ-CD, 10 mM DM-β-CD, 50 mM SDS, and 15% v/v acetonitrile as background electrolyte (BGE) (*see* **Notes 2–4**). Filter (0.22 or 0.45 μm) and sonicate before use.

6. *Sample solutions:* Prepare stock solutions of the imidazole drugs tioconazole, isoconazole, and fenticonazole (*see* **Note 5**) at a concentration of 1.0 mg/mL in methanol. For working solution of individual drugs, transfer 200 μL stock solution into a 1 mL volumetric flask and dilute to the mark with methanol. For the sample solution containing all three analytes, mix 200 μL of each solution and add 400 μL of methanol. Mix and filter (0.22 or 0.45 μm) before use.

3 Methods

1. Install capillary in the CE instrument according to the instructions of the manufacturer.
2. Condition a new capillary by subsequently rinsing with 0.1 M sodium hydroxide solution for 30 min and ultrapure water for 30 min.
3. Set the following instrument parameters:

   Capillary temperature: 30 °C.

   Detection wavelength: 200 nm (detection at the anodic end of the capillary).
4. Place run buffer vials in the carousel.
5. Apply separation voltage of 27 kV (normal polarity).
6. Flush capillary subsequently with run buffer for 15 min.
7. Place sample vial containing methanol in the instrument sample tray (*see* **Note 6**). Inject sample via electrokinetic injection at 3 kV for 3 s. Apply separation voltage and perform analysis.
8. Flush capillary subsequently with 0.1 M sodium hydroxide solution for 3 min, ultrapure water for 3 min, and run buffer for 5 min (*see* **Note 7**).
9. Subsequently, inject sample solution containing analytes (*see* **Note 8**) and inject triplicates. Between injections of samples follow the flushing sequence described in **step 8** before injection of the next sample. A typical electropherogram of the simultaneous enantioseparation of tioconazole, isoconazole, and fenticonazole is shown in Fig. 1.

4 Notes

1. Phosphate buffer is recommended since it is applicable over a wide pH range. In this regard, phosphate buffer (pH 7.0) is suggested for enantioseparation of the three analytes.
2. Run buffer is prepared from the addition of each components stock solution (reproducibility is acceptable). For easy

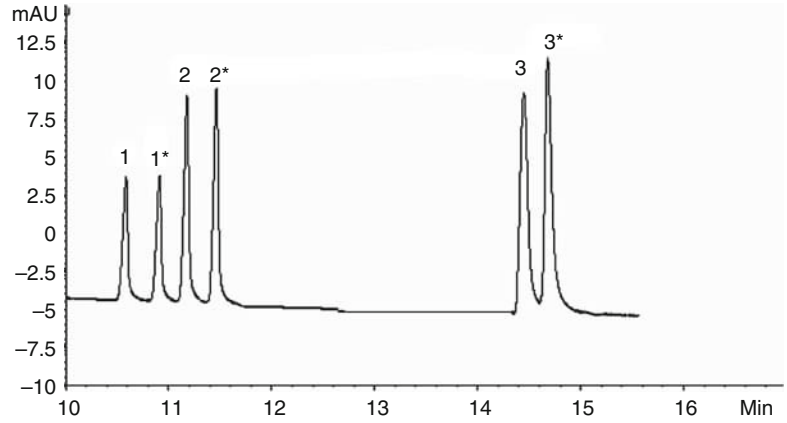

Fig. 1 Electropherograms of enantioseparation of the selected imidazole drugs at optimum CD-MEKC conditions. Separation conditions: 35 mM HP-γ-CD, 10 mM DM-β-CD, 35 mM phosphate buffer (pH 7.0), 50 mM SDS, 15% (v/v) acetonitrile, 27 kV separation voltage and 30 °C separation temperature. Analytes injected electrokinetically at 3 kV for 3 s. Peaks identification: 1, 1* = R-, S-tioconazole; 2, 2* = R-, S-isoconazole; 3,3* = R-, S-fenticonazole

handling, preparation of run buffer can be in a volume of 1.0 mL or larger. Even though insertion of BGE solution in a vial only requires microlitres (~200–300 μL), adequate volume is required for conditioning, analytical separation as well as renewal after three or four injections.

3. Example of preparation mixture of BGE with a total volume of 1.0 mL. The calculation of the individual components is described below. For the preparation of any given volume, multiply the respective μL volume with the number of the final desired volume in mL.

   Volume of phosphate buffer: 35 mM/500 mM (stock solution) × 1000 μL = 70 μL.

   Volume of HP-γ-CD: 35 mM/100 mM (stock solution) × 1000 μL = 350 μL.

   Volume of DM-β-CD: 10 mM/100 mM (stock solution) × 1000 μL =100 μL.

   Volume of SDS: 50 mM/500 mM (stock solution) × 1000 μL = 100 μL.

   Volume of 15% acetonitrile: 15% /100% × 1000 μL = 150 μL.

   Volume of water: 1000 μL − (70 + 350 + 100 + 100 + 150) μL = 230 μL

4. The background electrolyte compositions are under optimized conditions. The optimum values of each composition are

selected based on good resolution ($Rs > 1.5$), shorter migration time, and excellent peak efficiency ($N > 100{,}000$).

5. Samples from commercial vendors can be used. Certified standards of tioconazole, isoconazole nitrate, and fenticonazole nitrate can be obtained from the European Directorate for the Quality of Medicines and Healthcare (EDQM), Strasbourg, France.
6. To identify any system peak, preferably start run with sample solvent (methanol).
7. Flushing the capillary between consecutive run is crucial to avoid carryover and to ensure reproducible inner wall condition. If changing buffer shifts the migration time, extend the conditioning time to 10–15 min.
8. It is suggested to run individual enantiomers in triplicates in order to identify their migration order before performing simultaneous enantioseparation.

Acknowledgments

This work was supported by the Fundamental Research Grant Scheme from the Ministry of Higher Education (Malaysia) under vote number R.J130000.7826.3F262 (78314) and the National Science Foundation awarded by the Ministry of Science, Technology and Innovation (Malaysia) to S.M. Abdul Wahib is much appreciated.

References

1. Saz JM, Marina ML (2016) Recent advances in the use of cyclodextrins in the chiral analysis of drugs by capillary electrophoresis. J Chromatogr A 1467:79–94
2. Rezanka P, Navratilova K, Rezanka M, Kral V, Sykora D (2014) Application of cyclodextrins in chiral capillary electrophoresis. Electrophoresis 35:2701–2721
3. Zhu Q, Scriba GKE (2016) Advances in the use of cyclodextrins as chiral selectors in capillary electrokinetic chromatography: fundamentals and applications. Chromatographia 79:1403–1435
4. Huang L, Lin J, Xu L, Chen G (2007) Non aqueous and aqueous-organic media for the enantiomeric separations of neutral organophosphorus pesticides by CE. Electrophoresis 28:2758–2764
5. Li W, Zhao L, Zhang H, Chen X, Chen S, Zhu Z, Hong Z, Chai Y (2014) Enantioseparation of new triadimenol antifungal active compounds by electrokinetic chromatography and molecular modeling study of chiral recognition mechanisms. Electrophoresis 35:2855–2862
6. Terabe S, Otsuka K, Ichikawa K, Tsuchiya A, Ando T (1984) Electrokinetic separations with micellar solutions and open-tubular capillaries. Anal Chem 56:111–113
7. Terabe S (2008) Micellar electrokinetic chromatography for high-performance analytical separation. Chem Rec 8:291–301. The Japan Chemical Journal Forum and Wiley Periodicals, Inc.
8. Hu S-Q, Guo X-M, Shi H-J, Luo R-J (2015) Separation mechanisms for palonosetron stereoisomers at different chiral selector concentrations in MEKC. Electrophoresis 36:825–829
9. Van Zomeren PV, Hilhorst MJ, Coenegracht PMJ, De Jong GJ (2000) Resolution optimization in micellar electrokinetic chromatography

using empirical models. J Chromatogr A 867:247–259

10. Deeb SE, Iriban MA, Gust R (2011) MEKC as a powerful growing analytical technique. Electrophoresis 32:166–183
11. Lin X, Hou W, Zhou C (2003) Enantiomer separation of miconazole by capillary electrophoresis with dual cyclodextrin systems. Anal Sci 19:1509–1512
12. Česla P, Blomberg L, Hamberg M, Jandera P (2006) Characterization of anacardic acids by micellar electrokinetic chromatography and mass spectrometry. J Chromatogr A 1115:253–259
13. Wan Ibrahim WA, Warno SA, Aboul-Enein HY, Hermawan D, Sanagi MM (2009) Simultaneous enantioseparation of cyproconazole, bromuconazole, and diniconazole enantiomers by CD-modified MEKC. Electrophoresis 30:1976–1982
14. Menéndez-López N, Valimaña-Traverso J, Castro-Puyana M, Salgado A, García MA, Marina ML (2017) Enantiomeric separation of the antiuremic drug colchicine by electrokinetic chromatography: method development and quantitative analysis. J Pharm Biomed Anal 138:189–196
15. Hu S-Q, Wang G-X, Guo W-B, Guo X-M, Zhao M (2014) Effect of low concentration sodium dodecyl sulfate on the electromigration of palonosetron hydrochloride stereoisomers in micellar electrokinetic chromatography. J Chromatogr A 1342:86–91
16. Ibrahim WAW, Arsad SR, Maarof H, Sanagi MM, Aboul-Enein HY (2015) Chiral separation of four stereoisomers of ketoconazole drugs using capillary electrophoresis. Chirality 27:223–227
17. Pérez-Fernández V, García MA, Marina ML (2010) Enantiomeric separation of cis-bifenthrin by CD-MEKC: quantitative analysis in a commercial insecticides formulation. Electrophoresis 31:1533–1539
18. Yu T, Du Y, Chen B (2011) Evaluation of clarithromycin lactobionate as a novel chiral selector for enantiomeric separation of basic drugs in capillary electrophoresis. Electrophoresis 32:1898–1905
19. García MÁ, Menéndez-López N, Boltes K, Castro-Puyana M, Marina ML (2017) A capillary micellar electrokinetic chromatography method for the stereoselective quantitation of bioallethrin in biotic and abiotic samples. J Chromatogr A 1510:108–116
20. Kodama S, Nakajima S, Ozaki H, Takemoto R, Itabashi Y, Kuksis A (2016) Enantioseparation of hydroxyeicosatetraenoic acids by hydroxypropyl- γ-cyclodextrin-modified micellar electrokinetic chromatography. Electrophoresis 37:3196–3205
21. Orlandini S, Pasquini B, Caprini C, Del Bubba M, Douša M, Pinzauti S (2016) Enantioseparation and impurity determination of ambrisentan using cyclodextrin-modified micellar electrokinetic chromatography: visualizing the design space within quality by design framework. J Chromatogr A 1467:363–371
22. Mikuma T, Iwata YT, Miyaguchi H, Kuwayama K, Tsujikawa K, Kanamori T, Kana H, Inoue H (2016) Approaching over 10 000-fold sensitivity increase in chiral capillary electrophoresis: cation-selective exhaustive injection and sweeping cyclodextrin-modified micellar electrokinetic chromatography. Electrophoresis 37:2970–2976
23. Lin E-P, Lin K-C, Chang C-W, Hsieh M-M (2013) On-line sample preconcentration by sweeping and poly(ethylene oxide)-mediated stacking for simultaneous analysis of nine pairs of amino acid enantiomers in capillary electrophoresis. Talanta 114:297–303
24. Petr J, Ginterova P, Znaleziona J, Knob R, Loštáková M, Maier V, Ševčik J (2013) Separation of ketoprofen enantiomers at nanomolar concentration levels by micellar electrokinetic chromatography with on-line electrokinetic preconcentration. Cent Eur J Chem 11:335–340
25. Cheng H, Zhang Q, Tu Y (2012) Separation of fat-soluble isoquinoline enantiomers using β-cyclodextrin modified micellar capillary electrokinetic chromatography. Curr Pharm Anal 8:37–43
26. Ibrahim WAW, Wahib SMA, Hermawan D, Sanagi MM, Aboul-Enein HY (2012) Chiral separation of vinpocetine using cyclodextrin-modified micellar electrokinetic chromatography. Chirality 24:252–254
27. Hermawan D, Wan Ibrahim WA, Sanagi MM, Aboul-Enein HY (2010) Chiral separation of econazole using micellar electrokinetic chromatography with hydroxypropyl-γ-cyclodextrin. J Pharm Biomed Anal 53:1244–1249
28. Wan Ibrahim WA, Hermawan D, Sanagi MM, Aboul-Enein HY (2010) Stacking and sweeping in cyclodextrin-modified MEKC for chiral separation of hexaconazole, penconazole, myclobutanil. Chromatographia 71:305–309
29. Wan Ibrahim WA, Wahib SMA, Hermawan D, Sanagi MM, Aboul-Enein HY (2013) Separation of selected imidazole enantiomers using dual cyclodextrin system. Chirality 25:328–335