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Review

Enantioselective determination by capillary electrophoresis with cyclodextrins as chiral selectors

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Abstract

This review surveys the separation of enantiomers by capillary electrophoresis using cyclodextrins as chiral selector. Cyclodextrins or their derivatives have been widely employed for the direct chiral resolution of a wide number of enantiomers, mainly of pharmaceutical interest, selected examples are reported in the tables. For method optimisation, several parameters influencing the enantioresolution, e.g., cyclodextrin type and concentration, buffer pH and composition, presence of organic solvents or complexing additives in the buffer were considered and discussed. Finally, selected applications to real samples such as pharmaceutical formulations, biological and medical samples are also discussed.

Keywords: Enantiomer separation; Chiral selectors; Reviews; Cyclodextrin

Contents

1. Introduction 90
2. Cyclodextrins and their derivatives 90
   2.1. Analysis of cyclodextrins 91
3. Enantioseparation using cyclodextrins and parameters influencing the chiral resolution 92
   3.1. Cyclodextrin type, concentration and structure of analytes 93
   3.2. Effect of buffer pH, concentration and capillary temperature 95
   3.3. Effect of modifiers added to the BGE 96
      3.3.1. Addition of achiral surfactants 97
      3.3.2. Addition of organic modifiers 98
      3.3.3. Addition of other complexing agents 98
4. Method optimisation using CDs 99
5. Chiral CE separation compared with NMR and MS studies 100
6. Chiral electrochromatography 101
7. Applications 102
   7.1. Pharmaceutical analysis 102
   7.2. Biological and medical analysis 111
   7.3. Forensic analysis 112
   7.4. Miscellaneous 112
8. Conclusions 113
9. Abbreviations 117
References 118

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1. Introduction

The presence of asymmetric centre/s in many compounds of pharmaceutical, agrochemical, biochemical interest give rise to optical activity that can be responsible for the different properties of the enantiomers, e.g., biological, pharmacological, etc. Thus the demand for analytical methods possessing high efficiency and high resolution capability for enantiomers separation at low cost and short analysis time is increasing.

Analytical methods so far used for the analysis of chiral compounds include high-performance liquid chromatography (HPLC), thin-layer chromatography (TLC), gas chromatography (GC) and recently capillary electrophoresis (CE).

CE is a modern separation technique that provides rapid analysis with high efficiency and high resolution due to the use of high electric field and a variety of selective modes.

The use of CE for the separation of chiral compounds can be dated by the work of Gassmann et al. in 1985 with the separation of dansyl amino acid enantiomers [1]. Since this time a wide number of researchers investigated this topic utilising CE techniques for the separation of a large number of chiral compounds of interest in pharmaceutical, clinical, environmental fields.

A large number of review papers [2–20] and a specific book [21] document the increasing interest in chiral CE.

The separation of diastereoisomers can be achieved with a common employed background electrolyte (BGE) (achiral) while enantiomers can only be resolved by using chiral recognition agents. The list of chiral agents utilised in CE includes copper–amino acid complexes, antibiotics, chiral crown ethers, chiral micelles, proteins and cyclodextrins (CDs) or their derivatives. Among them CDs and their derivatives were widely investigated and applied for the enantiomers resolution of a large number of analytes, mainly of pharmaceutical interest.

The present paper reviews the state of the art of chiral separations obtained by CE techniques using CDs and their derivatives as the chiral recognition agent focusing the attention mainly on practical problems related with the selection of the appropriate CD and experimental conditions. Furthermore recent applications in pharmaceutical, clinical and environmental fields are also discussed.

2. Cyclodextrins and their derivatives

Cyclodextrins are oligosaccharides prepared by enzymatic degradation of starch and glycosyltransferases or cyclodextrinases producing a mixture of different CDs that can be separated by using, e.g., chromatography, crystallisation etc. [22]. They have a shape of a truncated cone with an open cavity, relatively hydrophobic and an outside hydrophilic due to the presence of hydroxyl groups (positions 2, 3 and 6 of glucopyranose). Nevertheless CDs with 6 to 12 glucose units have been separated, only those with six, seven and eight units (with the Greek names α-, β- and γ-CD, respectively) are currently used in analytical chemistry. The physical properties of the three native CDs are quite different, e.g., width of the cavity, solubility, molecular mass etc., however they possess the same depth [22].

Fig. 1 shows the chemical structure of β-CD while the main physical properties of α-, β- and γ-CDs are summarised in Table 1. As can be seen the solubility of β-CD is very low compared to that of the other

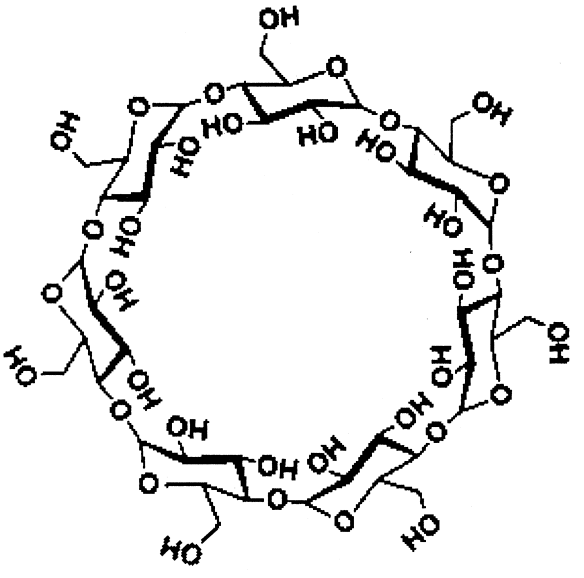


Fig. 1. Chemical structure of β-cyclodextrin.

Table 1
The main properties of native cyclodextrins

	CD type		
	α	β	γ
Number of glucose units	6	7	8
Molecular mass	972	1135	1297
Inner diameter (nm)	0.57	0.78	0.95
Depth (nm)	0.78	0.78	0.78
Solubility (g/100 ml water)	14.5	1.85	23.2
pK_a	12.33	12.20	12.08

reported oligosaccharides (<1.8%). However its solubility can be increased using, e.g., aqueous–organic solvents (methanol or ethanol, below 30%), high pH, urea as a BGE modifier [22,23], the wide number of β-CD derivatives etc. When selecting the above-mentioned organic additives, it should be considered that they compete with analytes in inclusion-complexation affecting the CE separation [24].

Based on published data it seems that the cavity of β-CD is appropriate to host a wide number of chemical compounds especially of pharmaceutical interest. Therefore the majority of the CD derivatives, commercially available, contain such CD in their composition.

In the inclusion-complexation process the analytes fit either completely or with their hydrophobic part into the CD cavity [22] entering through one of the two openings, primary and secondary with 6-hydroxyl and 2-, 3-hydroxyl groups, respectively [25].

The hydroxyl groups present on the rim of the CDs can be easily modified by chemical reactions in order to obtain CD derivatives with a different degree of substitution; the composition of the modified CD depends by several parameters such as reaction conditions, reagents type and ratio etc.

A wide number of CD derivatives are currently used in CE for chiral analysis and among them we can mention the uncharged methylated-, hydroxyethylated-, hydroxypropylated-, acetylated-CDs and the charged ones such as methylamino-, sulphobutylether-, carboxymethylated-, sulphated-, phosphated-CDs, etc.

The modified CDs can exhibit very different properties than the native ones, which can be easily used for improving the selectivity of the enantiomers separation, e.g., increased solubility, possibility for different secondary bonds, potentiality for the analysis of uncharged compounds, different hydrophobicity of the cavity, etc. For example, comparing β-CD and DM-β-CD, it can be observed that the presence of methoxy groups increases either the depth or the solubility of the last chiral selector. Charged/chargeable substituents of hydroxyls on the CD structure can be considerably helpful for CE method optimisation. In fact uncharged enantiomers can be moved to the detector as charged analytes due to the formation of inclusion-complexes with the modified CD. Furthermore the movement of the chiral selector in the opposite direction to that of selectant represents the ideal condition in order to achieve good resolution because causes an increase of the mobility difference between free and complexed analyte [26].

Finally, soluble CD polymers, obtained by reaction between β-CD or CM-β-CD and epichlorhydrin, were successfully employed in chiral CE [27–31].

2.1. Analysis of cyclodextrins

The analysis of CDs or their derivatives is of paramount importance in order to verify the purity of the material produced after the natural or synthetic preparation. Several separation methods were developed for the analysis of CDs including TLC, HPLC, spectroscopy, mass spectroscopy and recently CE [22,32–37].

The analysis of native CDs by CE is not easy because the compounds are not UV absorbing and do not possess charged/chargeable groups. However we demonstrated that CE could be a powerful tool for the analysis of such uncharged compounds. The analytes, after the injection, are moving to the detector by the electroosmotic flow (EOF) and since this driving force is not selective, they are not separated. However adding a negatively charged aromatic compound, e.g., benzoate (that moving in the opposite direction of the EOF) to the BGE we can achieve a selective retardation of the analytes if they possess different affinity for the anion. This was shown by us analysing α-, β- and γ-CDs using an indirect UV detection method. The three CDs reached with different mobility behind the EOF the detector displacing benzoate present in the BGE and

as a result negative peaks were recorded [33]. The method was later used for the analysis of charged CD derivatives (SBE-β-CD) [34]. Further studies were carried out for the analysis of charged CDs using CE–MS. The separated zones were detected using MS allowing the characterisation of the different species present in the mixture [37]. As an example of analysis of CDs, Fig. 2A and B show the electropherogram and the mass spectra of one peak, respectively, obtained analysing a sample of carboxymethylated γ-CD containing a mixture of different substituted cyclodextrin.

Other authors also studied the composition of the CDs used for electrophoretic separations in order to explain the different recognition capability of chiral selectors provided by different sources. Analysis of CD derivatives such as DM-β-CD, SBE-β-CD, SBE-γ-CD, CM-β-CD, using either CE and/or MALDI-TOF-MS and nuclear magnetic resonance (NMR) documents the different degree of substitution of the resolving agent usually used in CE [34,35,38–43].

Recent studies are currently dealing with the separation, characterisation and the use of a single CD isomer [44–49].

Tanaka and Terabe [50] used CE–MS for the characterisation of commercially available positively charged β-CD derivatives, namely quaternary ammonium and amphoteric β-CD (QA- and AM-β-CD, respectively). The analysis of QA-β-CD by indirect UV detection using pyridinium chloride as the absorbing co-ion revealed the presence of six peaks in the electropherogram of the analysed mixture clearly showing the presence of components with different degree of substitution. The mass spectra of the CD sample, obtained by flow injection, were very helpful to identify the different CDs present in the used mixture. On-line CE–MS was, recently used by Tanaka et al. [37] for the direct analysis of QA-β-CD and CM-γ-CD. Otsuka et al. [43] studied the effect of DM-β-CD (from five different suppliers) on chiral resolution of several enantiomers of pharmaceutical interest. The CDs were analysed by liquid chromatography finding two main components. The NMR and MS analyses revealed that the commercial CD derivative consisted of heptakis(2,6-di-*O*-dimethyl)-β-CD and hexakis(2,6-di-*O*-methyl)-mono-(2,3,6-tri-*O*-methyl)-β-CD.

3. Enantioseparation using cyclodextrins and parameters influencing the chiral resolution

Since two enantiomers possess similar physico–chemical properties, for a successful enantiomer

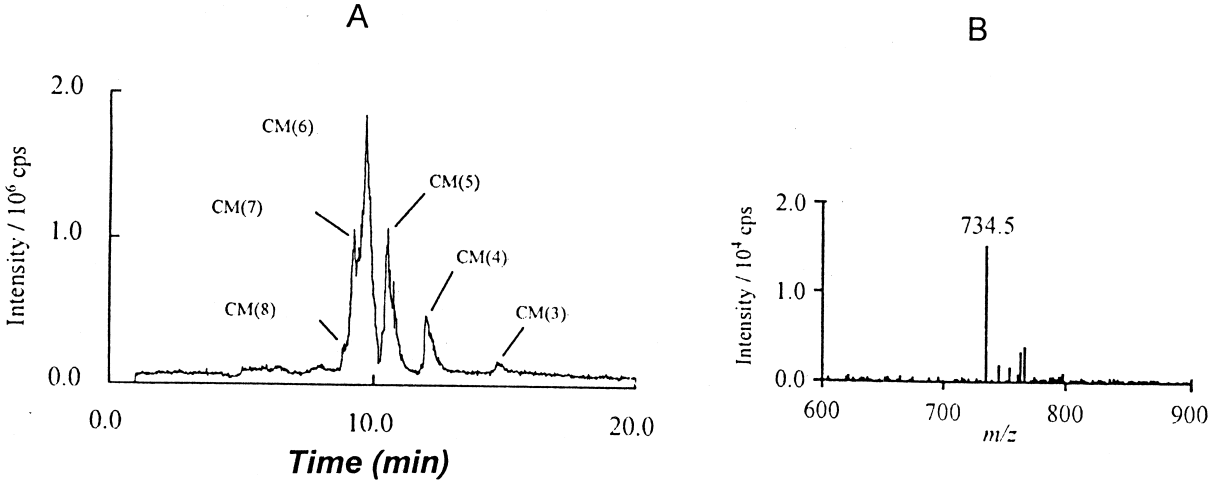


Fig. 2. TIC electropherogram of carboxymethylated γ-cyclodextrin (A) and mass spectra of the peak at 14.7 min. Experimental conditions: sample, 5 mg/ml; polyacrylamide coated capillary 80 cm×50 μm I.D.; background electrolyte, 40 m*M* ammonium acetate, pH 5.0; sheath liquid, background electrolyte–methanol (1:1) 5 μl/min; applied voltage −30 kV. CM(3–8) are the six different components of the CD mixture. The mass spectra (A) revealed the presence of $[CM(3)\text{-}\gamma\text{-}CD\text{-}2H]^{2-}$ (modified from Ref. [37]).

resolution in CE, it is necessary to selectively modify the effective mobilities of the two analytes. This can be obtained on forming stereoselective complexes where hydrophobic, hydrogen, π–π, dipole, van der Waals interactions can be involved.

In CE the separation of chiral compounds is achieved mainly by the direct separation method where the chiral selector is simply added to the BGE or bonded to either the capillary wall or to a stationary phase. Using CDs, analytes fit the cavity either with the whole molecule or with their hydrophobic part on forming inclusion-complexes stabilised by secondary bonds between the rim of the chiral selector and substituent groups of the analyte asymmetric centre. The complex formed during the electrophoretic process, in equilibrium with the free analyte, possesses a different mass responsible for the change of the effective mobility.

The enantioresolution can be influenced by several parameters such as the type and concentration of CD, pH and composition of the BGE, capillary temperature, applied voltage, additive to the BGE, etc.

Some of the experimental parameters influencing resolution and stereoselectivity will be briefly discussed in the next sections.

3.1. Cyclodextrin type, concentration and structure of analytes

As mentioned above α-, β- and γ-CD possess different dimensions of the cavity due to the number of glucopyranose in their structure. Since the inclusion-complexation mechanism is based on the possibility that a certain analyte fits into the cavity of the CDs, the shape and the size of both host and guest molecule are of paramount importance in the complexation mechanism. These effects were widely studied by several authors [51–61].

The importance of the CD type in the selection of the appropriate chiral resolving agent was demonstrated using different CE techniques (CGE, ITP, CZE) since 1988–1989 [51–53]. Several chiral drugs (pseudoephedrine, nor-pseudoephedrine, *O*-acetylpseudoephedrine and *p*-hydroxynorpseudoephedrine) were studied by ITP employing derivatised uncharged β-CD, namely DM-β-CD or TM-β-CD as chiral selectors added to the leading electrolyte (LE) [52].

Several dansyl amino acids enantiomers were studied by CGE using native CDs finding that the most appropriate chiral selector was γ-CD and the chiral resolution was strongly influenced by the CD concentration [51]. Different CDs (β-, DM-β- and TM-β-CD) were used in CZE for the enantiomers resolution of sympathomimetic drugs, namely ephedrine, nor-ephedrine, epinephrine, nor-epinephrine and isoproterenol. Among the CDs investigated the dimethylated derivative resulted to be the most effective resolving agent for all analytes allowing baseline resolution. The presence of both methoxy and hydroxyl groups on the secondary rim of the CD was fundamental in achieving the successful separations. We also found that the resolution of studied enantiomers increased by raising the concentration of the selector [53].

An interesting study dealing with the influence of CD type on chiral resolution was carried out by Yoshinaga and Tanaka [62] using different methylated β-CD for the enantioresolution of dansyl amino acids. The methylation of the CD in position 6 was not influencing the stereoselectivity while when the hydroxyl in position 2 was modified the chiral resolution was completely lost. These data show the key role of OH groups of the CD in the stereoselective mechanism for this type of compounds. The use of 2,3-dimethyl-β-CD improved the chiral resolving capability of the CD and caused a reversion of migration order. Also Miura et al. [63] demonstrated the importance of the type of CD used studying the chiral resolution of several herbicides enantiomers with selectively modified α-, β- or γ-CDs.

Recently several non-steroidal antiinflammatory drugs (NSAIDs) and phenoxypropionic acid herbicides (PPAHs) were resolved in their enantiomers using a novel positively charged β-CD, namely heptakis(6-methoxyethylamino-6-deoxy)-β-CD (Et-NH-β-CD). High chiral resolutions were achieved for indoprofen and fenoprofen ($R=11$ and 14, respectively). Baseline resolution was obtained for the separation of a mixture of six herbicide enantiomers [64].

The CD type was widely studied by Lin and co-workers presenting an extended screening project investigating 86 racemic drugs by CE utilising different CDs [65–68], e.g., using HP-β-CD 42 drugs of the 86 studied were resolved [65].

Interesting results can be achieved in chiral CE combining different CDs and this was shown by Tanaka et al. [55] for the separation of several dansylated amino acid enantiomers employing native CDs (β- or γ-CD). A combination of α- and β-CD was also used for the separation of 1,1′-binaphthyl-2,2′-dihylhydrogenphosphate (BDHP) and 1,1′-binaphthyl-2,2′-dicarboxylic acid (BDCA) enantiomers in the same run. Here α-CD was able to resolve only BDCA isomers [56,57].

The importance of the charge of the CD in the CE chiral separation process was shown by Terabe employing a positively charged CD [mono(6-amino-6-deoxy)-β-CD] for the chiral resolution of several dansyl amino acid enantiomers [54]. We investigated the effect of 6^{A}-methylamino-β-cyclodextrin on chiral resolution of several hydroxy acid enantiomers [69]. Sulphobutyl ether-β-cyclodextrin (SBE-β-CD) represents another important chiral selector widely used in CE. The modified chiral selector moves with its own electrophoretic mobility when the electric field is applied playing an important role in the separation process. Several studies demonstrated the potentiality of such CD resolving a wide number of chiral compounds [70–74]. In one of the above mentioned studies [70] the charged chiral selector was injected as a small zone prior to the sample (dimethindene enantiomers) obtaining interesting results even at low concentration of CD. The same group compared the effect of β-CD and sulphoalkylated-β-CD on chiral resolution of tricyclic antihistaminic drugs [75].

A mixture of randomly substituted sulphated CDs (degree of substitution, DS=7–10) were used by Stalcup and Gahm for the enantioseparation by CE of 56 pharmaceutical compounds including antidepressants, anticonvulsants, antimalarials, bronchodilators, etc. The separations were achieved reversing the polarity and using a BGE at pH 3.8 [76].

Besides the high-resolution capability of charged CDs in CE it is noteworthy to mention that peak tailing were very often observed especially at low pH analysing basic compounds [77]. This effect was less evident at pH 4 and using the CD with either one or four sulphobutyl substituents clearly showing the importance of the degree of substitution on enantioresolution. The influence of the degree of substitution was also studied for other negatively charged CDs such as CM-β-CD [78].

Recently sulphobutyl ether-β-cyclodextrin (SBE-β-CD) was found to be more effective than native or alkylated β-CD for the enantiomers resolution of functionalised piperidines. The addition of relative low concentration of this charged CD allowed achieving fast separation of dienomycine and 4-protected 2-alkylated piperidine [79].

Jakubetz et al. separated the enantiomers of hexobarbital using sulpho-*n*-propyl ether-β-CD (SPE-β-CD) and 2-hydroxy-3-trimethylamoniumpropyl ether-β-cyclodextrin (HTAP-β-CD) (anionic and cationic, respectively) finding a reversion of migration order. The second CD was used in polyacrylamide coated capillary and the *R*-isomer had the strongest interaction with the CD (first eluted). In this paper the authors also studied the dual chiral recognition mechanism using a coated capillary (Chirasil-Dex) and SPE- or HTAP-β-CD added to the mobile phase. An increase of enantioselectivity was observed when the second CD was present in the buffer [80].

The enantiorecognition capability of two new CD derivatives {6-deoxy-6-*N*-histamino-β-CD, hm-β-CD and 6-deoxy-6-[4-(2-aminoethyl)imidazolyl]-β-CD, mh-β-CD} was studied by Galaverna et al. [81] analysing several dansyl amino acids. The two CDs were positively charged and exhibited different enantioresolution. In fact higher resolutions were observed by using mh-β-CD towards the studied amino acid enantiomers. Furthermore an opposite migration order of the studied enantiomers was observed.

Recently a new family of single-isomer charged CDs was introduced by Vigh and co-workers for the enantiomers separation of either charged or uncharged analytes [46,47,49]. Besides heptakis(2,3-dimethyl-6-sulphato)-β-cyclodextrin forms less strong complexes with the studied analytes than the two single isomers [heptakis(2,6-diacetyl-6-sulphato)-β- and heptakis-6-sulphato-β-CD], it offers excellent stereoselectivity. The increase of CD concentration caused the reversal of migration order of studied neutral analytes. Weak bases or acids were resolved in their enantiomers at low and high pH [46]. Vincent and Vigh used heptakis-(2,3-diacetyl-6-sulphato)-β-cyclodextrin (HDAS-β-CD) for the chi-

ral resolution of carbidopa. Optimum experimental conditions were obtained using the charged resolving agent migration model showing the possibility to analyse minor enantiomer in L-carbidopa preparations with good results (short analysis time, reproducibility, etc.) [82].

A new modified β-CD derivatives, namely cyanoethylated-β-CD (β-CD-CN), was introduced in CE by us for the chiral resolution of either basic and acidic racemic compounds. The chiral selector possesses a relatively high solubility in water and organic solvents and compared to TM-β-CD exhibited a different stereoselective capability. In fact the migration order of *R*-naproxen was reversed when using β-CD-CN [83].

Mono-(5-glutamylamino-6-deoxy)-β-cyclodextrin (β-CD-Glu) is a zwitterionic cyclodextrin introduced by Lelievre et al. [84] for the enantiomer separation of uncharged analytes. The charge of the β-CD-Glu can be modulated selecting the appropriate buffer pH. In fact at low pH (2.3) the chiral selector was positively charged while at 10.3–11.2 the charge was negative. β-CD-Glu was successfully used in association with TM-β-CD for the chiral resolution of those enantiomers not separated by the first CD alone (e.g., carprofen).

We optimised a CE chiral separation method using CM-β-CD and comparing the results with those obtained with other native or derivatised CDs. The method was validated for the analysis of tramadol in tablets showing good linearity, accuracy, precision and recovery. A limit of detection (LOD) as low as $1 \cdot 10^{-7}$ *M* for each enantiomer was observed [85].

The CD concentration present in the running electrolyte used for the electrophoretic separation is fundamental in order to achieve successful and optimum experimental conditions. Very often, even if the addition of CD to the buffer is causing a decrease of effective mobility of enantiomers, no chiral resolution is obtained. One reason for the unsuccessful enantiomer separation can be due to the wrong selection of CD concentration, e.g., too high or too low than the optimum chiral selector concentration.

The effect of CD concentration on chiral resolution and/or enantioselectivity was widely studied usually finding that higher CD concentration causes an increase of chiral resolution with a maximum [86–90]. It is interesting to remark that in some cases the maximum of resolution is not observed (*R* increases by raising the CD concentration) because the CD cannot be dissolved at the desired concentration due to the low solubility.

Wren and Rowe [91] discussed theoretically the existence of an optimum CD concentration concluding that the maximum of resolution can be expected at CD concentration $=(K_1K_2)^{-1/2}$ where K_1 and K_2 are the stability constants of the CD–analytes complexes formed during the electrophoretic separation.

3.2. Effect of buffer pH, concentration and capillary temperature

The selection of the appropriate BGE (type of buffer and concentration, ionic strength, pH) is of paramount importance in order to achieve the optimum experimental conditions for a successful separation of enantiomers.

Three different types of electrophoresis separations can be involved in the chiral resolution of basic or acidic analytes. Desionoselective, ionoselective and duoselective are the three separation types. In the first case only the nondissociated enantiomer forms a selective complex with the CD. In the ionoselective case only the dissociated enantiomer is selectively complexed by the CD. Finally in the last type both nondissociated and dissociated compounds are involved in the selective complexation with the chiral selector [92]. The three separation types were widely discussed by Vigh and co-workers who proposed the mathematical model where both chiral selector concentration and pH of the BGE were considered. The model is of paramount importance for method optimisation in chiral CE because allows for the determination of optimum experimental conditions in a short time [92–97].

Thus the selection of the buffer pH should be done carefully in order to achieve the chiral resolution of studied enantiomers.

The ionic strength of the buffer influences both the EOF and the analyte migration time. Furthermore electromigration dispersion can be reduced increasing the ionic strength of the buffer [86]. However an increase of the current has to be expected. Gareil et al. [90] studied the effect of the ionic strength on chiral resolution of warfarin; the buffer [*N*-tris(hydroxymethyl)methyl-3-aminopropane sulphonate

(TAPS)] containing CD was at pH 8.35 and the ionic strength was increased adding sodium chloride. Lower electroosmotic flow, higher migration times and better resolutions were observed increasing the content of NaCl.

Experiments using relatively high concentration of the BGE (250 m*M* sodium acetate) were carried out achieving maximum of efficiency, resolution and selectivity for the enantiomers resolution of isoproterenol [98].

The chiral resolution of three profens, namely fenoprofen, ibuprofen and ketoprofen was carried out by Blanco et al. [99] in untreated capillaries using a phosphate–triethanolamine buffer at pH 5. The enantiomers separation was influenced by the CD concentration, buffer pH and capillary temperature. The effect of the buffer pH and concentration of the organic modifier on chiral resolution of propranolol and its metabolite enantiomers was also studied [100]. The influence of α-CD concentration, applied voltage and buffer pH on chiral separation of several underivatised amino acids was investigated [101]. Mexiletine enantiomers were resolved by CE employing TM-β-CD studying the effect of CD concentration, applied voltage and organic modifier [102].

The selection of the appropriate pH of the BGE allowed to achieve baseline resolution for 11 acidic racemates by using a commercially available positively charged β-CD derivatives (QA-β-CD). While dansyl amino acid enantiomers were resolved employing an amphoteric CD derivative AM-β-CD. The authors compared the results with those obtained analysing the same samples with uncharged CDs [50].

Among the new CD derivatives recently introduced in CE we can mention heptakis(6-hydroxyethylamino-6-deoxy-β-cyclodextrin) (β-CD-EA), a persubstituted CD with seven ethanolamine side arms at the primary rim. The change of the pH of the BGE influenced either the charge or the stereoselectivity of the separation of the studied compounds (good chiral resolutions were obtained in the pH range 4–7). Herbicides, dansyl amino acids, NSAIDs were the racemic mixtures separated in their enantiomers using the above mentioned CD derivative [103].

The effect of CD type, capillary temperature, type and concentration of polyethylene glycol on chiral resolution of terbutaline was studied [104]. The best results were achieved using 10 m*M* of hydroxyethyl-β-CD at 15°C; 0.1% (distomer/eutomer) was detected.

The capillary temperature is a very important parameter to be controlled in chiral analysis using electromigration methods. In fact the temperature is influencing several parameters. For example, the mobility of analytes, the kinetic and the thermodynamic of the inclusion-complexation with CDs, etc. The study of the effect of capillary temperature vs. chiral resolution and/or selectivity was carried out by several authors generally finding a reduction of either migration time [86,89,105–110] and resolution on increasing the temperature. In some cases the opposite was observed [111,112].

3.3. Effect of modifiers added to the BGE

The addition of achiral compounds to the BGE can be important in order to modify the electrophoretic mobilities of enantiomers allowing their separation by CE. The additives can influence several parameters such as the EOF, the viscosity, the solubility of either analytes and/or CDs, etc.

threo-Chloramphenicol and ketotifen enantiomers were separated using DM-β-CD with the addition of hydrophilic cellulose derivatives to the BGE. The improvement of resolution was ascribed to the decrease of EOF and to a reduction in adsorption of analytes on the capillary wall [113]. A similar effect was pointed out by Belder and Schomburg [114] studying the influence of polyvinyl alcohol (PVA) added to the BGE on chiral resolution of several tocainide compounds. Short chain alkyl ammonium cations strongly influenced the chiral resolution of several racemic drugs. Twenty-two compounds of pharmaceutical interest were studied with a buffer at pH 2.5 containing different CDs (β-CD, DM-β-CD, TM-β-CD and HP-β-CD) and TMA or TBA. The use of the additives caused a reversion of EOF with a general increase of migration time obtaining improvement in resolution, e.g., trimipramine was completely resolved using TBA [26]. Stalberg et al. improved the chiral separation of several local anaesthetic drugs with tetrapropylammonium (TPA) cations and TBA added to the buffer at pH 3

containing DM-β-CD [115]. Recently the influence of small organic cations in the BGE on chiral resolution of seven basic drugs was studied by Dong et al. [116]. Alprenolol, amphetamine, anisodamine, isoprenaline, pinacidil, synephrine and verapamil, were separated using HP-β-CD in the presence of Tris, triethanolamine, diethanolamine, triethanolamine, diethylamine or triethylamine. Among the additive used, triethylamine resulted to be the most effective in enhancing the chiral resolution.

3.3.1. Addition of achiral surfactants

Sodium dodecyl sulphate (SDS) is the most used surfactant forming micelles in CE for the enantiomers separation in presence of CDs. The method, called cyclodextrin-modified micellar electrokinetic chromatography (CD-MEKC) was firstly used by Terabe et al. [117] for the separation of hydrophobic achiral compounds such as chlorinated benzene congeners, polycyclic aromatic hydrocarbons, etc. Later on the CD-MEKC method was widely applied for the chiral separation of several compounds, e.g., derivatised amino acids [118–121], aromatase inhibitors and barbiturates [89], β-blockers [122], triazole derivatives [123,124], dihydropyridine derivatives [125], cycletanine [126], mephenytoin, phenytoin and their 4-hydroxy derivatives [127], derivatised peptides [128,129], pesticides [130], etc.

Fig. 3 shows a scheme of electrophoretic run of uncharged analytes by CD-MEKC.

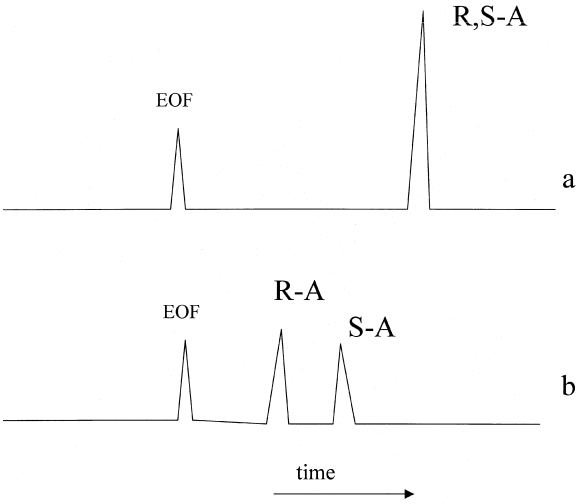
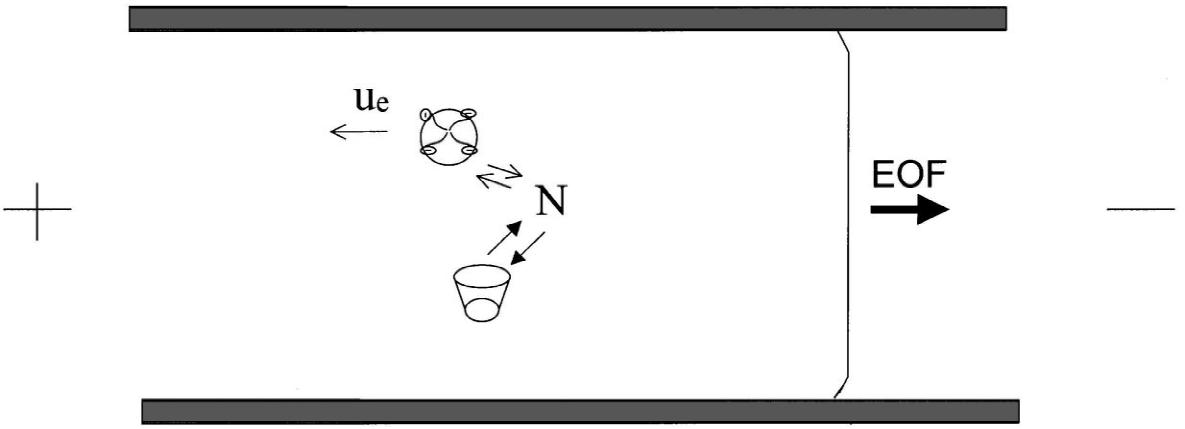


Fig. 4. Scheme of electrophoretic run of an uncharged racemic mixture (*R*,*S*-A) using (a) MEKC, (b) CD-MEKC. The separations are supposed to be carried out in the presence of sodium dodecyl sulphate, native CD, pH>7 and untreated capillary.

A micellar (SDS) and an aqueous phase containing the CD compose the system. A relatively high EOF transports the hydrophobic analytes to the detector (cathode) while SDS particles, negatively charged, possess their own mobility opposite to that of EOF. The analytes interact with SDS and CD modifying their mobility according to the different partition between the micellar and the aqueous phases. As can be seen in Fig. 4a and b the addition



EOF= electroosmotic flow; u_e= electrophoretic mobility; = SDS

Fig. 3. CD-MEKC scheme of the electrophoretic run of uncharged analytes in aqueous and micellar phase containing cyclodextrins.

of native uncharged CDs to the BGE containing micelles causes a decrease of retention time of analytes due to interaction with the chiral selector with a baseline enantiomers resolution.

The first paper dealing with enantiomers separation using CD-MEKC was shown by Nishi et al. [131] studying the effect of several CDs, namely α-, β-, γ-, DM-β- and TM-β-CD added to the buffer at pH 9.0 containing 50 m*M* SDS and 4 *M* of urea on chiral resolution thiopental, pentobarbital, phenobarbital, barbital. The CD type (especially the cavity size) influenced the chiral recognition. In fact γ-CD, with the biggest cavity, was the most effective chiral resolving agent. The inclusion-complexation analyte–CD was responsible for the chiral recognition and the CD with the widest cavity was necessary probably due to inclusion of both analytes and surfactant

Furthermore the addition of other chiral additives together with CDs, e.g., L-methoxyacetic acid or D-camphor-10-sulphonate enhanced the chiral resolution of the studied compounds.

The above mentioned work can serve here as an example documenting the usefulness of CD-MEKC method where several parameters can be easily modified for improving the stereoselectivity, e.g., surfactant type and concentration, CD type and concentration, buffer type, pH, ionic strength, organic modifier etc. A detailed discussion of CD-MEKC chiral separation can be found in another part of this special issue.

3.3.2. Addition of organic modifiers

The addition of organic modifiers to the BGE can modify several parameters such as the stability constants of the inclusion-complexes, the EOF, the analysis time, the conductivity of the BGE, the solubility of either analytes and/or the CD. Thus the enantiomers resolution can be either improved or decreased depending on the type of analyte studied. Several authors observed an improvement of chiral resolution using methanol, e.g., Guttman et al. achieved the chiral resolution of several dansyl amino acids adding 10% of organic modifier to the BGE containing CD in a polyacrylamide gel filled capillary [51], propranolol was resolved in its enantiomers only modifying the BGE (phosphate buffer–urea–β-CD) with 10–30% of the above mentioned modifier [87]. Improvement on enantiomer resolution, adding methanol to the BGE, was also recorded for mandelic acid [109], warfarin [90], and imidazole derivatives [132]. Theoretical considerations concerning the effect of organic modifier on chiral resolution were reported by Wren and Rowe [133]. The authors concluded that the organic modifier reduces the binding constants of chiral analytes and when the CD concentration is at or below the optimum value (maximum of resolution), causes a decrease of the mobility differences of enantiomers. This was also shown by Penn et al. [134] adding cyclohexanol to the BGE containing CDs for the enantiomer separation of thioconazole. The addition of the organic modifier to the BGE caused a decrease of the binding constants of (−)-, (+)-thioconazole with β-CD (from 1320 and 1600 M^{-1} to 223 and 259 M^{-1}, respectively) due to the competition in the inclusion-complexation organic modifier–analyte with CD.

Besides the positive effect using organic modifiers in CE in several cases a decrease in enantioseparation was observed, e.g., clenbuterol [135], denopamine and trimetoquinol [136], deprenyl [137], dioxypromethazine [138]. Recently dansyl-phenylalanine, leucine and propranolol were separated using β-CD as the chiral selector in BGEs containing C_1–C_6 alcohols observing a decrease of chiral selectivity [139].

CDs were also used in 100% of organic solvents achieving good enantiomer resolutions; here the resolution mechanism is mainly based on adsorption interactions with the rim of the chiral selector [140,141].

Recently heptakis(2,3-diacetyl-6-sulphato)-β-CD (HDAS-β-CD), a single isomer, was used in nonaqueous (100% methanol) CE separation of several weak basic enantiomers of pharmaceutical interest achieving very good resolutions. Very weak complexation between neutral or acidic enantiomers and the CD was observed [48].

3.3.3. Addition of other complexing agents

Non-polar primary amines are very difficult to separate in their enantiomers using CDs alone in capillary electrophoresis, however the combination with 18-crown-6-ether (18-crown-6) can be advan-

tageously used in order to achieve or improve chiral resolution. This effect was shown by Huang et al. [142] analysing six amines with DM-β-CD or HE-β-CD or γ-CD in the presence of 18-crown-6. Here the analyte is complexed by both additives of the BGE and the CD recognises the chiral centre of the amine. As an example Fig. 5 show the chiral separation and the chemical structure of 1-amminotetralin using DM-β-CD-crown either separated or in mixture. The same authors also separated the 1-methyl-3-phenylpropylamine enantiomers combining γ-CD and 18-crown-6-ether. Here the chiral centre is too far from the aromatic ring for a successful chiral discrimination using CD alone.

Cationic ion pairing reagent, quinine, resulted to be a powerful tool in influencing the separation of several acid and basic enantiomers with CDs [143].

The mechanism of CE enantioseparation using a combination of 18-crown-6 and CDs was also studied by Armstrong et al. [144]. A wide number of analytes containing amine functional group were separated using β-CD or its derivatives in presence of 30 m*M* of achiral crown ether.

An interesting example of combination of chiral selector with non chiral complexing agent was shown by Schmid et al. [145]. Borate buffer supported with β-CD or succinyl-β-CD allowed the separation of phenyl-1,2-ethanediol, 3-benzyloxy-1,2-propanediol, hydroxybenzoin, 3-(*N*-benzyl-*N*-methylamino)-1,2-propanediol. The borate anion was the complexing agent of vicinal diols.

4. Method optimisation using CDs

Considering the wide number of CDs used in CE and commercially available it is very difficult to find a general rule for the selection of the appropriate experimental parameters. However a method development strategy for chiral CE analysis employing

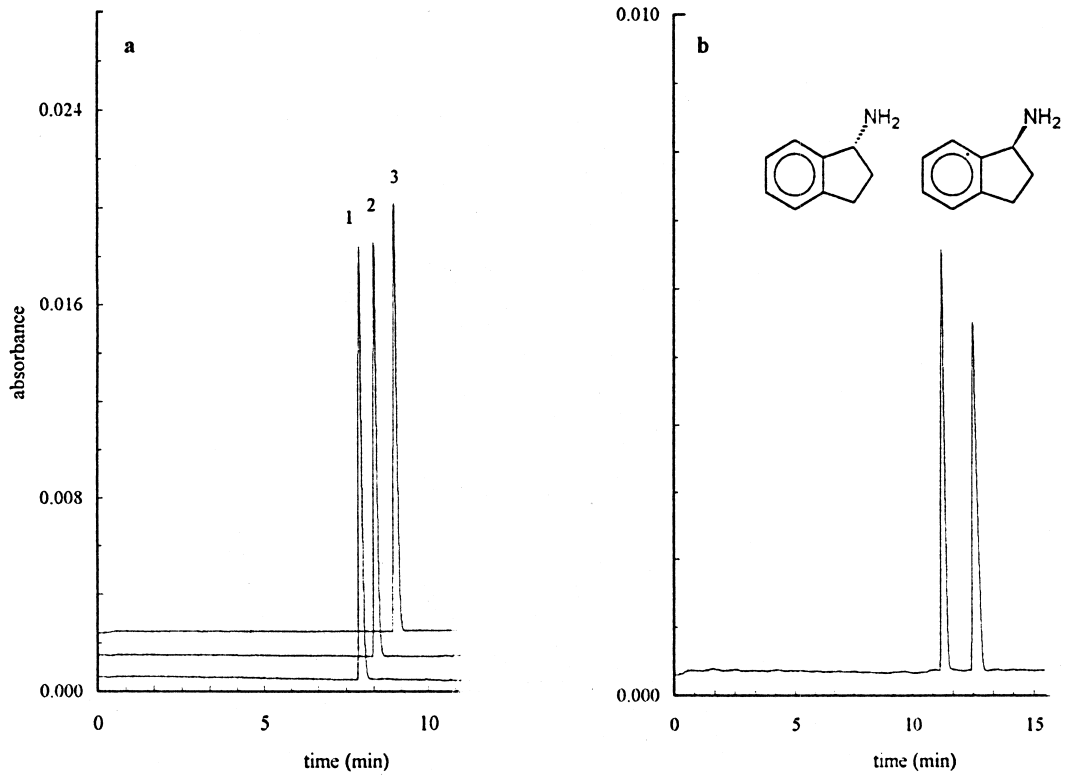


Fig. 5. Electropherogram of the enantiomers separation of 1-aminoindan by CE. 50 m*M* phosphate, pH 2 containing: (a) 1, no additive; 2, 5 m*M* 18-crown-6; 3, 5 m*M* DM-β-CD, (b) 5 m*M* 18-crown-6 and 5 m*M* DM-β-CD (modified from Ref. [142]).

CDs was proposed [146–148]. The following section will give some advice to be considered for method optimisation for the chiral separation by CE using CDs as the chiral selector.

Based on the data reported in previous sections, employing CDs, it can be remarked that the chiral resolution is based on inclusion-complexation stabilised by secondary bonds. Thus the chemical structure of analytes, their shape and size have to be carefully observed in order to select the appropriate CD. Analytes with linear chain can fit the CD with the smallest width, e.g., α-CD while β-CD can be very effective when one or two aromatic rings are present. Furthermore α-CD can form inclusion-complexes with analytes containing only one aromatic ring (or more than one but not condensed), however the presence of substituent groups in *ortho* or *meta* positions can cause a reduction of complexation due to hindrance effect. A more complex analyte structure (e.g., three or four aromatic rings) can be resolved using γ-CD.

When using native CDs the enantiomer separation is not achieved, attention should be paid to the wide number of derivatised CDs (more expensive than native ones). In this case uncharged and/or charged compounds are available. The charge of the CDs should be generally opposite to that of analytes in order to maximise the difference of mobility between free and complexed analyte. Furthermore charged chiral selectors can be selected when uncharged enantiomers have to be separated avoiding the use of micelles.

Another important step for method optimisation is the selection of the appropriate electrophoretic mechanism and experimental conditions. The knowledge of the solubility of the analyte is very important in order to select the appropriate organic solvent, while the choice of the buffer pH can be done considering if the analyte is basic or acidic (verify the p*K* or observe the effective mobility at different pH levels). For basic compounds, an acidic pH (2.5–3.5) and a native CD can be selected; negatively charged chiral selectors were also successfully used, however, in such conditions, peak dispersion can be observed. Excellent chiral resolution of basic compounds, using negatively charged CDs, were achieved increasing the pH of the BGE or using single chiral selector isomers.

In the case of acidic compounds a buffer at pH higher than the pK_a of analytes is generally used and the electrophoretic run performed in coated capillary (reversing the polarity). A different approach was proposed by Fillet et al. [149] using a buffer at pH 3 (phosphoric acid titrated with triethanolamine) and reversing the polarity. The acidic analytes were migrating to the anode as uncharged compounds moved by the EOF. The enantioresolution was achieved using negatively charged CDs, e.g., SBE-β-CD or CM-β-CD. It is interesting to remark that at the above-mentioned conditions the EOF has the same direction of analytes allowing their separation in a shorter time. The authors suggested to use 5–10 m*M* of CD, however in the case of unsuccessful resolution a dual chiral system can be used (uncharged and charged CDs).

5. Chiral CE separation compared with NMR and MS studies

A comparative study of CE and NMR for the enantiomer separation of dimethindene (an antihistaminic drug) was discussed by Chankvetadze et al. considering several charged and uncharged CDs. Using native β-CD and CM-β-CD as the chiral selectors, the migration order of dimethindene enantiomers was reversed. By NMR studies the authors demonstrated that a multimodal complexation analyte–CM-β-CD take place [150].

Recently Chanvetadze et al. [151] observed different chiral ability for native β-CD, CM-β-CD and TM-β-CD analysing racemic chlorpheniramine (CHL). The use of charged CD allowed to achieve very good resolution even at very low chiral selector concentration (1 mg/ml), however the migration order with TM-β-CD was opposite to that with β-CD and CM-β-CD. NMR and MS were used for preliminary investigations to obtain information about the stoichiometry of the complexes formed were also carried out.

Heptakis(2,3-di-*O*-acetyl)-β-cyclodextrin (2,3-Dac-β-CD) and γ-CD were used for the chiral resolution of the four stereoisomers of fencamfamine by CE. Good resolution was obtained with the two chiral selectors and NMR experiments revealed that

the analytes interact mainly with the outside region of the CD cavity [152].

Naproxen enantiomers were separated using a new CD derivative (cyanoethylated-β-CD) by CE and the results compared with those obtained by ^{1}H-NMR where a more pronounced chemical shift for H-3, H-5 and H-7 was observed. It was concluded that naproxen fit the CD cavity interacting with the H proton at position 3,4, 5 and 7. However conclusions concerning the stereoselective interactions could not be given [83].

The use of CE–MS when CDs are employed as the chiral additive to the BGE can give rise to some drawbacks that can deteriorate the signal of the detector. Thus the appropriate experimental condition when using such chiral selector have to be carefully optimised. This was shown by Schulte et al. [153] using a charged CD (CM-β-CD) for the separation of etilefrine, mianserine, dimethindene and tropic acid. The movement of the CD, opposite to that of analytes allowed avoidance of the contamination of the ion source of ESI-MS.

Similar approach was studied by Tanaka et al. [154] for the chiral separation of camphorsulphonic acid, tropic acid enantiomers using DM-β-CD and QA-β-CD, respectively.

Javerfalk et al. [155] separated ropivacaine and bupivacaine enantiomers by CE–MS using TM-β-CD in a coated capillary with a partial filling method avoiding interferences in the ion source. With the optimised method the authors could detect 0.25% of *R*-ropivacaine in presence of an excess of *S*-enantiomer. Otsuka et al. [156] employed CE–MS for the chiral separation of phenoxy acid herbicides, TM-β-CD was the chiral selector. Besides good results were obtained, the authors concluded that further investigations about the contamination of ion-source of the MS would be carried out.

6. Chiral electrochromatography

Capillary electrochromatography (CEC) is a recent electrophoretic technique mainly used for the analysis of uncharged compounds. However separation of chiral compounds was also demonstrated employing CDs as the chiral selector.

The separation of chiral compounds was achieved in CEC using two different approaches, namely packed or open capillaries. In the first mode the capillary contains a chiral stationary phase while in open tubular CEC (OTCEC) the chiral selector is adsorbed or covalently bonded to the capillary wall. Therefore when using the second mode, several drawbacks are avoided (frits preparation and bubble formation)

Both methods require complicated manipulations due to chemical reactions and/or packing procedure. The analytes are carried to the detector by the EOF (with a flat flow profile) which allows obtaining higher efficiency than HPLC where the profile is parabolic. As CEC is a very recent CE separation method, only a few papers were published, however its potential is very promising.

Mayer and Schurig [157] firstly discussed the use of enantioseparations by OTCEC employing a modified capillary with permethylated β-cyclodextrin (Chiralsil-Dex). Using the above mentioned chiral selector in a 50 μm I.D. capillary the authors separated the enantiomers of BDHP and phenylethanol [157].

The same authors used another CD bonded to the capillary wall (permethyl-γ-CD) for the chiral resolution of non steroidal anti-inflammatory drugs, namely ibuprofen, flurbiprofen and cicloprofen. The influence of buffer pH, applied voltage and film thickness was widely studied. The efficiency decreased by increasing the film thickness while α increased [158].

β- or γ-CD polymers were immobilised on the capillary wall and used for the separation of epinephrine enantiomers and the best results were achieved using the γ-CD [159].

Micro packed CEC was used for the separation of several racemic compounds employing a modified silica support with permethylated β-CD. A BGE at pH 7, containing a phosphate buffer–methanol or acetonitrile (90:10), was the mobile phase. Good efficiency and resolution were achieved in a relatively short time (10–20 min) for mephobarbital, hexobarbital, pentobarbital, benzoin, gluthetimide, methyl mandelate. The increase of organic modifier concentration in the mobile phase caused a reduction of the chiral resolution [160].

Recently Wei et al. [161] separated phenylephrine and synephrine enantiomers by CEC on bare silica

stationary phase using HP-β-CD as the chiral mobile phase additive. The mobile phase did not contain the organic modifier in order to enhance the complexing capability of the CD used.

7. Applications

Although the number of publications dealing with the use of CDs in CE for the resolution of chiral compounds is relatively high, applications to the analysis of real samples are few. The work done up to this time was mainly focused on (i) finding new CDs, (ii) theory, (iii) method optimisation, (iv) separation of model samples. A list of enantiomers resolved by CE using CDs as chiral selector can be found in previously published reviews [5,9,11,13,162,163]. Table 2 shows the latest chiral separations grouped in accord to the CD type used for electrophoretic experiments. This table does not report applications to real samples.

In this section we will discuss about the analysis of chiral compounds in real samples of interest in pharmaceutical, medical, biological and environmental fields mainly discussing the reports appeared in the last 2 years.

7.1. Pharmaceutical analysis

Heptakis-2,6-di-*O*-methyl-β-CD was used by us for the qualitative analysis of two commercial formulations containing (−)-epinephrine as the main component. The presence of 1% and 35% of (+)-epinephrine was found in the two samples. The separation was carried out by using an acidic BGE and a polyacrylamide coated capillary in less than 10 min [230]. Later on Peterson and Trowbridge employed the same CD for quantitative determination of the two enantiomers of epinephrine in pharmaceutical formulations (of different age). Good precision and reproducibility were demonstrated by using the peak area ratio (the internal standard was pseudoephedrine). The samples contained (−)-epinephrine as the main compounds and 1.3–2.3% of its antipode as the impurity [231].

Chiral CE can be advantageously used for the chiral purity control of drugs due to the high-resolution capability and high efficiency of the technique. This was shown by Nishi et al. analysing the pharmacological inactive form, *R*-trimetoquinol, used as bronchodilator drug. The optimised method employed an uncharged β-CD polymer detecting 0.1% of the impurity [28].

The use of a BGE at pH 2.5 supplemented with trimethylated-β-cyclodextrin (TM-β-CD) allowed the baseline resolution of D- and L-*m*-fenfluramine. The drug was used for the treatment of obesity and the pharmacological activity is mainly due to the L-antipode [232].

Qualitative and quantitative analysis of (*Z*)- and (*E*)-tamoxifen enantiomers in pharmaceutical preparation was performed using β-CD. The tablets of Novaldex were dissolved in methanol and the solution injected for the electrophoretic analysis. An impurity of (*E*)-tamoxifen was found in one of the two analysed samples [233].

CE was successfully used for monitoring the synthetic process leading to the preparation of pure enantiomeric drug (cisolirtine). The racemic drug was crystallised using (+)- or (−)-di-*p*-toluoyltartaric acid. Several CDs were studied in order to find the optimum experimental conditions (CD type and concentration, buffer type, pH and concentration) and among them HP-β-CD resulted to be the best chiral selector allowing baseline resolution of the two studied enantiomers [234].

Vincent and Vigh used a single isomer sulphated cyclodextrin for the CE analysis of the minor component of L-carbidopa. Very good separation selectivity was obtained selecting the pH of the BGE at 2.5 and a capillary temperature of 16°C. The CD concentration was selected at the level where both L- and D-carbidopa change from cationic to anionic due to the complexation with the chiral selector. The optimised method was reproducible and validated for the analysis of the minor component [82].

The simultaneous separation and quantitation of pheniramine, chlorpheniramine and bromopheniramine enantiomers was carried out by Wu et al. using a phosphate buffer at pH 3.5 containing β-CD and the anionic polymer (carboxymethylated) β-CD. Good results were achieved and the assay of dexchlorpheniramine maleate in tablets was performed [235]. Fillet and co-workers demonstrated the possibility to analyse NSAID enantiomers, *S*-naproxen, in tablets using a BGE at low pH (phos-

Table 2
Latest chiral separations grouped in accordance to the CD type used for electrophoretic experiments

Compounds	CE type	CD	BGE	Ref.
Tryptophan	CZE	α-CD	40 m*M* Tris–phosphoric acid, pH 2.4 and 75 m*M* C.S.	[164]
Phenylalanine, tryptophan, tyrosine	CZE	α-CD	0.1 *M* phosphoric acid–$HClO_4$, pH 2.5 and 10–40 m*M* C.S.	[101]
Anesthetics (ketamine, prilocaine)	CZE	α-CD	46 m*M* phosphoric acid, pH 2.9 and 50 m*M* C.S.	[165]
Phenprocoumon	CZE	α-CD	120 m*M* Britton Robinson, pH 7 and 15 m*M* C.S.	[147]
Anesthetics (mepivacaine, prilocaine)	CZE	β-CD	46 m*M* phosphoric acid, pH 2.9, 5 *M* urea and 15–80 m*M* C.S.	[165]
Alkyl guanidine *N*-carboxylates arpromidine-type guanidines	CZE	β-CD	125 m*M* sodium phosphate, pH 2–3, 5 *M* urea and 100–125 m*M* C.S.	[166]
Peptides (FLEC derivatives, Gly)	CD-MEKC	β-CD	40 m*M* HEPES–Tris, pH 7.5–40 m*M* SDS–15% 2-propanol and 25 m*M* C.S.	[129]
Menadione hydrogensulphite	CZE	β-CD	50 m*M* phosphate, pH 4 and 15 m*M* C.S.	[50]
Chlorpheniramine	CZE	β-CD	100 m*M* phosphoric acid–triethanolamine, pH 3 and 18 mg/ml C.S.	[151]
Dimethindene	CZE	β-CD	50 m*M* potassium phosphate, pH 3 and 15 m*M* C.S.	[150]
Phenyl-1,2-ethanediol 3-benzyloxy-1,2-propanediol hydrobenzoin 3-(*N*-benzyl-*N*-methylamino)-1,2-propanediol	CZE	β-CD	50 m*M* borate buffer, pH 9.3 and 1.8% C.S.	[145]
Non-steroidal antiinflammatory drug (flobufen)	CD-MEKC	β-CD	20 m*M* phosphate–borate, pH 9, 5% urea, 100 m*M* SDS and 20 m*M* C.S.	[167]
N-oxide (*N*-*n*-butyl-*N*-methylaniline, pargyline)	CZE	β-CD	150 m*M* lithium phosphate buffer, pH 2.5 and 15 m*M* C.S.	[168]
3-Phenyllactic acid	CZE	β-CD	50 m*M* phosphate, pH 4 and 10 m*M* C.S.	[50]
2-Phenoxypropionic acid	CZE	β-CD	50 m*M* phosphate, pH 4 and 10 m*M* C.S.	[50]
Benzodioxane compounds	CZE	β-CD	100 m*M* phosphoric acid–triethanolamine, pH 3 and 1–15 m*M* C.S.	[169]
Phenyl-1,2-ethanediol, 3-benzyloxy-1,2-propanediol, several quinazolinone	CZE	β-CD	50 or 100 m*M* borate, pH 9.3 and 1.8% C.S.	[170]
Salsolinol	CEC	β-CD	20 m*M* sodium phosphate, pH 3, 5 m*M* sodium 1-heptanesulphonate and 12 m*M* C.S.	[171]
Benzylmethylphenylsulphonium, benzylmethyl-*p*-tolylsulphonium			0.1 *M* sodium phosphate, pH 2.5, 50 m*M* TBA and 5 m*M* C.S.	
Methyl-, ethyl-, propyl-, butyl-, pentyl-benzylphenylsulphonium	CZE	β-CD	The same system+30% methanol	[172]
	CZE	β-CD		[172]
threo-2-Amino-1-(4-nitrophenyl)-1-3-propanediol, threo-2-(dimethylamino)-1-(4-nitrophenyl)-1,3-propanediol	CZE	β-CD	0.04-0.20 *M* NaOH and 12 m*M* C.S.	[173]
Anisodamine, chlorpheniramine, propranolol, isoprenaline	CZE	β-CD–β-CD polymer	80 m*M* Tris–phosphate, pH 3–5	[174]
Amines alkyl guanidine *N*-carboxylates arpromidine-type guanidines	CZE	γ-CD	125 m*M* sodium phosphate, pH 2.5, 5 *M* urea and 125-250 m*M* C.S.	[166]
Amino acid derivatives (FITC-tryptophan, citruline, methionine, serine, homoserine, tyrosine, phenylalanine, threonine, histidine, leucine, norleucine, isoleucine, valine, norvaline, asparagine, arginine, ornithine, lysisne, aspartic acid, glutamic acid, proline)	MEKC	γ-CD	100 m*M* borate buffer, pH 9.5, 30 m*M* SDS and 10 m*M* C.S.	[175]

(*Continued on next page*)

Table 2 (*continued*)

Compounds	CE type	CD	BGE	Ref.
Mandelic acid	CZE	γ-CD	50 m*M* phosphate, pH 4 and 120 m*M* C.S.	[50]
Menadione hydrogensulphite	CZE	γ-CD	50 m*M* phosphate, pH 4 and 20 m*M* C.S.	[50]
Peptides (FMOC derivatives, Ala, Gly–Met, Gly–Phe; APOC–Gly)	CD-MEKC	γ-CD	40 m*M* phosphate, pH 7.5–40 m*M* SDS–15% 2-propanol and 12 or 8 m*M* C.S.	[129]
Pesticides (dialifos, malathion, dichlorprop methyl ester)	CD-MEKC	γ-CD	20 m*M* borate, pH 9–100 m*M* SDS–organic modifier and 40–60 m*M* C.S.	[130]
Venlafaxine	CZE	γ-CD	100 m*M* borate, pH 9.2 and 10 m*M* C.S.	[176]
Warfarin	CZE	γ-CD	50 m*M* phosphate, pH 6 and 120 m*M* C.S.	[50]
Warfarin	CZE	γ-CD	120 m*M* Britton Robinson, pH 7 and 15 m*M* C.S.	[147]
Carprofen, cicloprofen, fenoprofen, naproxen, warfarin	CZE	β-CD-CN	75 m*M* Britton Robinson, pH 5 and 2.5–30 m*M* C.S.	[83]
Clenbuterol, epinephrine, etilefrin, isoproterenol, terbutaline, norphenylephrine	CZE	β-CD-CN	75 m*M* Britton Robinson, pH 2.5 and 20–100 m*M* C.S.	[83]
Chlortalidone	CZE	β-CD-NH_2	39.1 m*M* phosphate–18 m*M* ammediol, pH 2.3 and 5 m*M* C.S.	[177]
Amino acids, dansyl (α-aminobutyric, valine)	CZE	2,3-Dac-β-CD	0.1 *M* sodium borate–0.05 *M* sodium phosphate, pH 9 and 10 m*M* C.S.	[178]
Fencamfamine	CZE	2,3-Dac-β-CD	0.05 *M* phosphate, pH 4.5 and 12 m*M* C.S.	[152]
Phenylethylamines (norephedrine, methylephedrine, 4-hydroxynorephedrine, 4-hydroxyamphetamine, oxilofrine, oxedrine, etilephrine, orciprenaline, terbutaline)	CZE	2,3-Dac-β-CD	0.1 *M* potassium dihydrogenphosphate, pH 4.5 and 3 m*M* C.S.	[179]
Amino acids, α-naphthalenesulphonyl- or β-naphthalenesulphonyl-alanine, leucine, norleucine, norvaline, valine, α-aminobutyric acid	CZE	2,6-DM-γ-CD	0.1 *M* sodium borate–0.05 *M* sodium phosphate, pH 9 and 10 m*M* C.S.	[180]
Amino acids, α-naphthalenesulphonyl- or β-naphthalenesulphonyl-alanine, leucine, norleucine, norvaline, valine, α-aminobutyric acid	CZE	3,6-DM-γ-CD	0.1 *M* sodium borate–0.05 *M* sodium phosphate, pH 9 and 10 m*M* C.S.	[180]
Amino acids, dansyl (asparagine, α-aminobutyric, glutamic, serine, valine, norleucine, leucine, phenylalanine)	CZE	AM-β-CD	50 m*M* phosphate, pH 6 and 10 m*M* C.S.	[50]
Bromopheniramine, chlorpheniramine, doxylamine, pheniramine	CZE	CE-β-CD	20 m*M* phosphate, pH 5.8 and 14 m*M* C.S.	[60]
Amlodipine	CZE	CM-β-CD	50 m*M* Na_2HPO_4, pH 3 and 2.5 m*M* C.S.	[181]
Anisodamine, ketamine, isoprenaline	CZE	CM-β-CD	75 m*M* phosphoric acid–Tris, pH 5 and 7.5 m*M* C.S.	[58]
Aspartyl dipeptides (Asp–PheOMe, β-Asp–PheOMe, Asp–$PheNH_2$, β-Asp–$PheNH_2$)	CZE	CM-β-CD	50 m*M* phosphate, pH 3.3 and 15 m*M* C.S.	[182]
Chlorpheniramine	CZE	CM-β-CD	100 m*M* phosphoric acid–triethanolamine, pH 3 and 1 mg/ml C.S.	[151]
Dimethindene	CZE	CM-β-CD	50 m*M* potassium phosphate, pH 3 and 1 m*M* C.S.	[150]
Dipeptides (Asp–Phe–NH_2, Asp–Phe–OMe)	CZE	CM-β-CD	50 m*M* phosphate, pH 3.3 and 15 mg/ml C.S.	[183]
Epinephrine	CZE	CM-β-CD	111 m*M* Britton Robinson, pH 7 and 9 m*M* C.S.	[184]
Etilefrine, mianserine, dimethindene	CZE	CM-β-CD	10 m*M* acetic acid–ammonium acetate, pH 3.5 and 0.2–3 mg/ml C.S.	[153]
Oxamniquine	CZE	CM-β-CD	50 m*M* Na_2HPO_4, pH 3 and 15 m*M* C.S.	[42]
Tramadol	CZE	CM-β-CD	50 m*M* phosphate–Tris, pH 2.5 and 5 m*M* C.S.	[85]
Amino acids, AQC (Arg, Lys, His)	CZE	CM-β-CD polymer	10 m*M* BTP, pH 7 and 0.5% C.S.	[185]

Table 2. (*continued*)

Compounds	CE type	CD	BGE	Ref.
Propranolol and its main metabolites	CZE	CM-β-CD–β-CD	52 m*M* borate–30 m*M* sodium acetate acetic acid, pH 8.7, 4 *M* urea, 20% methanol, 6.69 and 30 m*M* C.S.	[186]
1-Benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine	CZE or CD-MEKC	DM-β-CD	50 m*M* phosphate, pH 3 and 5 m*M* C.S. or 50 m*M* phosphate, pH 3, 40 m*M* SDS and 65 m*M* C.S.	[187]
3-(3-Carboxyphenyl)alanine, 3-carboxyphenylglycine, 3-(3-carboxy-4-hydroxyphenyl)alanine, phenylalanine, tryptophan	CZE	DM-β-CD	40 m*M* phosphate and 60 m*M* C.S.	[188]
Amino acids, AQC (Ala, Val, Ile, Met, Pro, Cys, Lys, Ser, Thr, Asn, Gln, Phe, Trp, Tyr, His)	CZE	DM-β-CD	10 m*M* BTP, pH 7 and 5 m*M* C.S.	[185]
Benzodioxane compounds	CZE	DM-β-CD	100 m*M* phosphoric acid–triethanolamine, pH 3 and 1–60 m*M* C.S.	[169]
Chlorpheniramine	CZE	DM-β-CD	100 m*M* phosphoric acid–triethanolamine, pH 3 and 50 mg/ml C.S.	[151]
Chlorprenaline, epinephrine, norepinephrine, phenylephrine, synephrine,	CZE	DM-β-CD	20–50 m*M* Tris–phosphoric acid, pH 3.24 and 10–16 m*M* C.S.	[189]
Dimethindene	CZE	DM-β-CD	50 m*M* potassium phosphate, pH 3 and 25 m*M* C.S.	[150]
Epinephrine, isoproterenol, β-hydroxyohenethylamine, octopamine	CZE	DM-β-CD	100 m*M* sodium phosphate–methanol (90:10), pH 2.5, 5 *M* urea and 20 m*M* C.S.	[190]
Galanthamine, narwedine, *N*-ethyl-nawedine, 1-bromo-*N*-ethyl-narwedine	CZE	DM-β-CD	50 m*M* tetrabutylammoniumdihydrogenphosphate, pH 2.5 and 30 m*M* C.S.	[191]
Imazaquin	CZE	DM-β-CD	50 m*M* sodium acetate, pH 4.6 and 10 m*M* C.S.	[192]
Lobeline and lobeline analogs	CZE	DM-β-CD	100 m*M* phosphate, pH 2.7 and 25 m*M* C.S.	[193]
Mandelic acid	CZE	DM-β-CD	50 m*M* phosphate, pH 4 and 20–80 m*M* C.S.	[50]
Melatonergic drugs (191602, 191435, 195387)	CZE	DM-β-CD	50 m*M* phosphate, pH 2.58 and 28 m*M* C.S.	[194]
Oxedrine	CZE	DM-β-CD	120 m*M* Britton Robinson, pH 3 and 10 m*M* C.S.	[147]
Terbutaline, ketamine	CE-MS	DM-β-CD	5 m*M* ammonium acetate–0.8 *M* acetic acid in methanol–water (80:20) and 5 or 15 m*M* C.S.	[195]
Vanilmandelic acid	CZE	DM-β-CD	50 m*M* phosphate, pH 4 and 40 m*M* C.S.	[50]
Warfarin	CZE	DM-β-CD	50 m*M* phosphate, pH 6 and 5 m*M* C.S.	[50]
Warfarin	CZE	DM-β-CD	100 m*M* sodium dihydrogenphosphate–methanol, pH 8.4 (98:2) and 8 m*M* C.S.	[164]
1-Phenylethylamine, 1-(1-naphthyl)ethylamine, 1-aminoindan, 2-amino-3-phenylpropanol, 3-(*p*-chlorophenoxy)-2-hydroxypropylamine, phenylalanine, 3-fluorophenylalanine, tyrosine	CZE	DM-β-CD and 18-crown-6 (10 m*M*)	50 m*M* phosphate, pH 2 and 5–10 m*M* C.S.	[196]
1-Aminoindan	CZE	DM-β-CD and 18-crown-6 (10 m*M*)	50 m*M* phosphate, pH 2 and 5 m*M* CD	[142]
1,2,3,4-Tetrahydro-1-naphthylamine	CZE	DM-β-CD and 18-crown-6 (10 m*M*)	50 m*M* phosphate, pH 2 and 5 m*M* CD	[142]
2-Amino-1,2-diphenylethanol, 1-aminoindan, *cis*-1-amino-2-indanol, 2-amino-3-phenyl-1-propanol, 3-amino-3-phenyl-propionic acid, 4-chlorophenylalaninol, α-methyltryptamine, 1-(1-naphthyl)ethylamine, phenylalanine, 1,2,3,4-tetrahydronaphthylamine	CZE	DM-β-CD–30 m*M* 18-crown-6	50 m*M* sodium dihydrogenphosphate, pH 2.2 and 20 m*M* C.S.	[144]
Dichlorprop	CZE	EtCa-β-CD	100 m*M* acetic acid–sodium acetate, pH 5 and 12.5 m*M* C.S.	[197]
PPAH (mixture of six racemic herbicides)	CZE	Et-NH-β-CD	50 m*M* NaH_2PO_4, pH 6 and 3 m*M* C.S.	[64]

(*Continued on next page*)

Table 2 (*continued*)

Compounds	CE type	CD	BGE	Ref.
Non-steroidal antiinflammatory drugs (fenoprofen, flurbiprofen, ketoprofen, carprofen, ibuprofen, indoprofen, suprofen)	CZE	Et-NH-β-CD	50 m*M* NaH_2PO_4, pH 5–7 and 2–20 m*M* C.S.	[64]
Carbidopa	CZE	HDAS-β-CD	25 m*M* phosphoric acid–triethylamine, pH 2.5, 8% polyethylene glycol 900 and 20 m*M* C.S.	[82]
19 Neutral, basic, acidic and zwitterionic racemic compounds	CZE	HDAS-β-CD	Buffer at, pH 2.5 or 9.5 with 10–50 m*M* C.S.	[198]
2-Indanol, benzoin, 2-phenyl butyric acid, 2-phenyl pentanol, 1-phenyl pentanol, tryptophan, propranolol, dansyl tryptophan	CZE	HDMS-β-CD	25 m*M* phosphoric acid triethylamine–15–50% methanol and 100 m*M* C.S.	[49]
N-Oxides (*N*-methyl-*N*-*n*-propylaniline, *N*-*n*-butyl-*N*-methylaniline, pargyline)	CZE	HE-β-CD	150 m*M* lithium phosphate buffer, pH 2.5 and 50 m*M* C.S.	[168]
Terbutaline	CZE	HE-β-CD	100 m*M* sodium phosphate, pH 2.5, polyethylene glycol 2000 and 10 m*M* C.S.	[104]
2-Phenyl-1-propylamine	CZE	HE-β-CD and 18-crown-6 (10 m*M*)	100 m*M* phosphate, pH 2 and 10 m*M* CD	[142]
1-Aminoindan	CZE	HE-β-CD and 18-crown-6 (10 m*M*)	100 m*M* phosphate, pH 2 and 10 m*M* CD	[142]
1,2,3,4-Tetrahydro-1-naphthylamine	CZE	HE-β-CD and 18-crown-6 (10 m*M*)	100 m*M* phosphate, pH 2 and 10 m*M* CD	[142]
Non-steroidal antiinflammatory drugs (carprofen, cicloprofen, flurbiprofen, indoprofen, ketoprofen, naproxen, suprofen)	CZE	Hepta-MeNH-β-CD	75 m*M* Britton Robinson, pH 5 and 5 m*M* C.S.	[199]
Alimemazine, alprenolol, atropine, baclofen, benproperine bromphenamine, bupivacaine, carazolol, cicletanine, clenbuterol, clobutinol, doxylamine, homatropine, ketamine, mefloquine, mepindolol, metaclazepam, metipranolol, naftidrofuryl, nefopam, nicardipine, norfenefrine, ofloxacin, orphenadrine, oxprenolol, phenoxybenzamine, phenylpropanolamine, pindolol, prilocaine, procyclidine, promethazine, tetryzoline, trihexyphenidyl, zopiclone	CZE	HP-α-CD	100 m*M* sodium dihydrogenphosphate, pH 2.5 and 45 m*M* C.S.	[200]
Amino acid derivatives, dansyl aspartic acid dansyl-α-aminocaprilic acid, 2-phenoxypropionic acid, dansyl phenylalanine, naphthylethylamine, terbutaline	CD-MEKC	HP-β-CD	50 m*M* phosphate, pH 7–SDS and C.S.	[121]
Amlodipine	CZE	HP-β-CD	50 m*M* Na_2HPO_4, pH 3 and 20 m*M* C.S.	[181]
Amphetamine, phenylephrine	CZE	HP-β-CD	100 m*M* Tris–phosphoric acid, pH 2.3 and 12 m*M* C.S.	[201]
Anesthetics (bupivacaine, mepivacaine, ropivacaine)	CZE	HP-β-CD	46 m*M* phosphoric acid, pH 2.9 and 50 m*M* C.S.	[165]
Benzodioxane compounds	CZE	HP-β-CD	100 m*M* phosphoric acid–triethanolamine, pH 3 and 1–60 m*M* C.S.	[169]
Bromopheniramine, chlorpheniramine,	CZE	HP-β-CD	50 m*M* phosphate, pH 3.24 and 28 m*M* C.S.	[60]
Chlorpheniramine	CZE	HP-β-CD	100 m*M* phosphoric acid–triethanolamine, pH 3 and 36 mg/ml C.S.	[151]
Clorprenaline, esmolol	CZE	HP-β-CD	50 m*M* phosphate, pH 2.5 and 15 m*M* C.S.	[202]
p-Chlorowarfarin	CZE	HP-β-CD	50 m*M* phosphate, pH 6 and 5 m*M* C.S.	[50]
Econazole	CZE	HP-β-CD	50 m*M* phosphate–triethanolamine, pH 2.5 and 15 m*M* C.S.	[203]
Imazamethabenz	CZE	HP-β-CD	50 m*M* sodium acetate, pH 4.6 and 10 m*M* C.S.	[192]

Table 2 (*continued*)

Compounds	CE type	CD	BGE	Ref.
N-Oxides (*N*-methyl-*N*-*n*-iso-propylaniline, *N*-*n*-butyl-*N*-methylaniline, pargyline)	CZE	HP-β-CD	150 m*M* lithium phosphate buffer, pH 2.5 and 50 m*M* C.S.	[168]
Pesticides (melathion, ruelene)	CD-MEKC	HP-β-CD	20 m*M* borate, pH 9–100 m*M* SDS–65 m*M* C.S.	[130]
2-Phenyllactic acid	CZE	HP-β-CD	50 m*M* phosphate, pH 4 and 40 m*M* C.S.	[50]
3-Phenylbutyric acid	CZE	HP-β-CD	50 m*M* phosphate, pH 5 and 1 m*M* C.S.	[50]
Phenyramidol, sotalol	CZE	HP-β-CD	40 m*M* phosphoric acid–10 m*M* TBA, pH 2 and 20 m*M* C.S.	[204]
Propranolol	CZE	HP-β-CD	40 m*M* Tris–phosphoric acid, pH 2.4 and 10 m*M* C.S.	[164]
Propranolol	CE-MS	HP-β-CD	5 m*M* ammonium acetate–0.8 *M* acetic acid in methanol–water (80:20) and 20 m*M* C.S.	[195]
Tropic acid	CZE	HP-β-CD	50 m*M* phosphate, pH 5 and 10 m*M* C.S.	[50]
Vanilmandelic acid	CZE	HP-β-CD	50 m*M* phosphate, pH 4 and 120 m*M* C.S.	[50]
Venlafaxine	CZE	HP-β-CD	100 m*M* borate, pH 9.2 and 4 m*M* C.S.	[176]
Warfarin	CZE	HP-β-CD	50 m*M* phosphate, pH 6 and 10 m*M* C.S.	[50]
2-Amino-1,2-diphenylethanol, 1-aminoindan, *cis*-1-amino-2-indanol, 2-amino-3-phenyl-1-propanol, 3-amino-3-phenyl-propionic acid, blacofen, clenbuterol, diphenylethylenediamine, β-hydroxyphenethylamine, α-methylbenzylamine, α-methyltryptamine, 1-(1-naphthyl)ethylamine, octopamine, phenylalanine, 1,2,3,4-tetrahydronaphthylamine, tryptophan butyl ester	CZE	HP-β-CD–30 m*M* 18-crown-6	50 m*M* sodium dihydrogenphosphate, pH 2.2 and 30 m*M* C.S.	[144]
22 Neutral, basic, acidic and zwitterionic racemic compounds	CZE	HS-β-CD	Buffer at, pH 2.5 or 9.5 and 10–50 m*M* C.S.	[45]
Hexobarbital	CZE	HTAP-β-CD	20 m*M* borate–phosphate, pH 7 and 25 m*M* C.S.	[80]
Tramadol, *O*-demethylated tramadol, *N*-demethylated tramadol, pethidine	CZE	methyl-β-CD (DS=1.8)	50 m*M* phosphate buffer, pH 2.5, 220 m*M* urea, 15 m*M* triethylamine and 75 m*M* C.S.	[205]
Bupivacaine, mepivacaine, prilocaine, ropivacaine	CZE	methyl-β-CD (DS=10.4-14.7)	phosphate, pH 3 I=0.04 and 36–76 m*M* C.S.	[206]
Orciprenaline	CZE	methyl-β-CD (DS=10.5-14.7)	phosphate (I=0.04), pH 3 and 7.6 m*M* C.S.	[207]
Disopyramide, tocainide	CZE	Phos-γ-CD	BGE, pH 2.4 or 6.8 and 7 m*M* C.S.	[208]
Metoprolol, tocainide	CZE	Phos-α-CD	BGE, pH 4.9 or 6.8 and 15 m*M* C.S.	[208]
Mephobarbital, hexobarbital, pentobarbital, 5-ethyl-1-methyl-5-(*n*-propyl)barbituric acid, benzoin, α-methyl-α-phenylsuccinimide, gluthetimide, MTH-proline, methyl mandelate	CEC	PM-β-CD	5 m*M* phosphate, pH 7–methanol (4:1) CD-modified silica	[160]
Adrenocrome semicarbazone sulphonate, 4-bromomandelic acid, *p*-chlorowarfarin, chrisanthemum monocarboxylic acid, menadione hydrogensulphite, 2-phenylbutyric acid, 2-phenyllactic acid, 2-phenoxypropionic acid, tropic acid	CZE	QA-β-CD	50 m*M* phosphate buffer, pH 4–7 and 0.3–5 m*M* of C.S.	[50]
Carprofen, fenoprofen amino acids (dansyl: aminobutyric, glutamic, leucine, methionine, norleucine, norvaline, phenylalanine, serine, threonine, tryptophan, valine	CZE	QA-β-CD	20 m*M* ammonium acetate+1% acetic acid in formamide, pH* 7.1 and 20 m*M* C.S.	[141]

(*Continued on next page*)

Table 2 (*continued*)

Compounds	CE type	CD	BGE	Ref.
Labetalol, nafronyl, nefopam, propiomazine, promethazine, propranolol	CZE	QA-β-CD	0.01 *M* sodium borate, 0.1% PVA, pH 11.52 and 10 m*M* C.S.	[209]
Tropic acid	CZE	QA-β-CD	40 m*M* ammonium formate, pH 5 and 5 m*M* C.S.	[154]
Amlodipine	CZE	SBE-β-CD	50 m*M* Na_2HPO_4, pH 7 and 1 m*M* C.S.	[181]
Chloroquine, pemoline	CZE	SBE-β-CD	50 m*M* sodium phosphate, pH 3 and 0.5–2.5 m*M* C.S.	[210]
Dienomycine, functionalised piperidine	CZE	SBE-β-CD	63.6 m*M* phosphoric acid–46.9 m*M* sodium hydroxide, pH 2.6 and 5–25 mg/ml C.S.	[79]
Dimethindene	CZE	SBE-β-CD	50 m*M* potassium phosphate, pH 3 and 1 m*M* C.S.	[150]
Ephedrine, methylphenyloxazolidinone, pseudoephedrine, trolox	CZE	SBE-β-CD	20 m*M* Tris–phosphate, pH 2.5 and 1.5 m*M* C.S.	[59]
Herbicides (bromacil, chlorbufam, ethofumesate, flamprop, haloxyfop, dluazifop	CZE	SBE-β-CD	25 m*M* borate, pH 9 and 5–50 mg/ml C.S.	[211]
Norephedrine, norpseudoephedrine, ephedrine, pseudopehedrine, amphetamine, methamphetamine	CZE	SBE-β-CD	13.4 m*M* phosphate, pH 8.5–methanol (90:10) and 10 m*M* C.S.	[212]
Oxamniquine	CZE	SBE-β-CD	50 m*M* Na_2HPO_4, pH 7 and 3 m*M* C.S.	[42]
LY213829 sulphoxide metabolite	CZE	SBE-β-CD–β-CD	50 m*M* lithium hydroxide–phosphoric acid, pH 2.5 and 10/7 m*M* C.S	[213]
Amino acids derivatives, dansyl (leucine, valine, norvaline)	CZE	SBE-γ-CD	20 m*M* phosphate, pH 7–10% MeOH and 2.5 m*M* C.S.	[41]
Binaphtol	CZE	SBE-γ-CD	20 m*M* phosphate, pH 7–10% MeOH and 2.5 m*M* C.S.	[41]
Secobarbital	CZE	SBE-γ-CD	20 m*M* phosphate, pH 7–15% MeOH and 215 m*M* C.S.	[41]
1-(9-Antrhryl)-2,2,2-trifluoroethanol	CZE	SBE-γ-CD	20 m*M* phosphate, pH 7–2 *M* urea and 15 m*M* C.S.	[41]
Dimethindene	CZE	SEE-β-CD	50 m*M* potassium phosphate, pH 3 and 2 m*M* C.S.	[150]
Hexobarbital	CZE	SPE-β-CD	20 m*M* borate–phosphate, pH 7 and 1 m*M* C.S.	[80]
1-Aminoindan, 1-aminotetralin	CZE	Su-β-CD	40 m*M* phosphate, pH 7 and 2.3 m*M* C.S.	[214]
Chlorpheniramine	CZE	Su-β-CD	100 m*M* phosphoric acid–triethanolamine, pH 3 and 2 mg/ml C.S.	[151]
Dipeptide (Asp-Phe-OMe, Asp-Phe-NH_2)	CZE	Su-β-CD	37.5 m*M* triethylammonium phosphate, pH 2.2 and 5% C.S.	[215]
Disopyramide, laudanosine, nadolol, tetrahydrozoline, norephedrine, indapamide, propranolol, nafronyl, mepenzolate, doxylamine, chlorpheniramine, ethopropazine, chorphedianol, labetalol, primaquine	CZE	Su-β-CD	10 m*M* $Na_2B_4O_7$, pH 11.57, 0.1% polyvinyl alcohol and 20 m*M* C.S.	[216]
Ethopropazine, labetalol, mianserine, nafronyl, promethazine, propranolol, acebutolol, nadolol	CZE	Su-β-CD	50 m*M* Tris–phosphoric acid, pH 2.5, 0.1% polyvinyl alcohol and 1–20 m*M* C.S.	[216]
Ethyl-, butyl-, pentyl-, methylphenylsulphonium	CZE	Su-β-CD	0.1 *M* sodium phosphate, pH 2.5, 50 m*M* TBA and 4 m*M* C.S.	[172]
1-Hydroxy-1,4-dimethyltetralin, 1-hydroxy-1,2-dimethyltetralin, 2-hydroxy-1-methyltetralin, 1-methyl-2-tetralone, 4-methyl-1-tetralone, 1-carboxy-3-indanone, 1-carboxy-3-indanol	CZE	Su-β-CD	40 m*M* phosphate, pH 3.3 and 6.5 m*M* C.S.	[214]
1-Hydroxy-1-methyltetralin	CZE	Su-β-CD	40 m*M* phosphate, pH 3.1 and 6.5 m*M* C.S.	[214]
1-Indanol, 1-hydroxytetralin, 1,4-dihydroxyindan, 1-hydroxy-5-methylindan, 1-hydroxy-6-methoxyindan, 1,5-dihydroxytetralin, 1-hydroxy-4-methyltetralin, 1-hydroxy-5,7-dimethyltetralin, 1-hydroxy-7-methyltetralin	CZE	Su-β-CD	40 m*M* phosphate, pH 4.1, 6.5 m*M* C.S.	[214]

Table 2 (*continued*)

Compounds	CE type	CD	BGE	Ref.
Labetalol, propranolol	CZE	Su-β-CD	30 m*M* phosphate, pH 6.5 amd 10.3 mg/ml C.S.	[217]
Norephedrine, norpseudoephedrine, amphetamine, methamphetamine	CZE	Su-β-CD	13.4 m*M* phosphate, pH 8.5–methanol (90:10) and 10 m*M* C.S.	[212]
Ormeloxifene	CZE	Su-β-CD	10 m*M* sodium phosphate, pH 3 and 2% C.S.	[218]
Terbutaline	CZE	Su-β-CD	25 m*M* phosphate, pH 3, 5–25% methanol and 2% C.S.	[219]
Tryptophanamide	CZE	Su-β-CD	10 m*M* Tris–citric acid, pH 2.3 and 5 m*M* C.S.	[220]
Tropa alkaloids (atropine, homatropine, ipratropium	CZE	Su-β-CD	50 m*M* phosphate buffer, pH 1.5–10 and 3–15 m*M* C.S.	[221]
1-Methylindan, 1-methyltetralin, 1-methylbenzosuberan	CZE	Su-β-CD and γ-CD	40 m*M* phosphate, pH 4.5, 6.5 and 21.1 m*M* C.S.	[214]
1-Hydroxytetralin	CZE	Su-β-CD and γ-CD	40 m*M* phosphate, pH 3.9, 6.5 and 5.8 m*M* C.S.	[214]
1-Hydroxy-2-methyltetralin	CZE	Su-β-CD and HP-β-CD	40 m*M* phosphate, pH 3.9, 6.5 and 19.2 m*M* C.S.	[214]
Adrenaline, denopamine, chlorpheniramine, noradrenaline, timepidium, trimetoquinol	CZE	Su-β-CD–α- or β- or γ-CD	100 m*M* phosphate–triethylamine, pH 3 and 10 m*M*–10–20 m*M* C.S.	[222]
Hexobarbital, pentobarbital, secobarbital, chlormezanone, chlortalidone, mephenytoin	CZE	Su-β-CD–DM- or TM-β-CD	100 m*M* phosphoric acid-triethanolamine, pH 3 or 5 and 5 m*M*/10 m*M* C.S.	[223]
Chlorpheniramine	CZE	SUC-β-CD	100 m*M* phosphoric acid-triethanolamine, pH 3 and 18 mg/ml C.S.	[151]
Dimethindene	CZE	SUC-β-CD	50 m*M* potassium phosphate, pH 3 and 15 m*M* C.S.	[150]
Phenyl-1,2-ethanediol 3-benzyloxy-1,2-propanediol hydrobenzoin 3-(*N*-benzyl-*N*-methylamino)-1,2-propanediol phenylethanol	CZE	SUC-β-CD	50 m*M* borate buffer, pH 9.3 and 1.8% C.S.	[145]
Norephedrine, norpseudoephedrine, ephedrine, pseudopehedrine, amphetamine, methamphetamine	CZE	Su-γ-CD	13.4 m*M* phosphate, pH 8.5–methanol (90:10) and 10 m*M* C.S.	[212]
Adrenocrome	CZE	TM-β-CD	50 m*M* phosphate, pH 4 and 80 m*M* C.S.	[50]
Amino acids, PTH (Ile, Pro, Trp)	CD-MEKC	TM-β-CD	(10 m*M* formic acid, 50 m*M* SDS)–methanol (95:5) and 25–50 m*M* C.S.	[224]
Anesthetics (bupivacaine, ketamine, mepivacaine, prilocaine, ropivacaine)	CZE	TM-β-CD	46 m*M* phosphoric acid, pH 2.9 and 26–153 m*M* C.S.	[165]
Anesthetics (bupivacaine, ropivacaine)	CE–MS	TM-β-CD	50 m*M* acetic acid, pH 3 and 100 mg/ml C.S.	[155]
Atropine and eight synthetic derivatives	CZE	TM-β-CD	50 m*M* Tris–phosphate, pH 2.8 and 10–40 m*M* C.S.	[225]
Benzhexol, esmolol	CZE	TM-β-CD	50 m*M* phosphate, pH 2.5 and 15 m*M* C.S.	[202]
Bencynonate	CZE	TM-β-CD	50 m*M* sodium phosphate, pH 2.5 and 15 m*M* C.S.	[203]
Chlorpheniramine	CZE	TM-β-CD	100 m*M* phosphoric acid–triethanolamine, pH 3 and 80 mg/ml C.S.	[151]
Diclofop	CZE	TM-β-CD	50 m*M* sodium acetate, pH 4.6 and 10 m*M* C.S.	[192]
Dimethindene	CZE	TM-β-CD	50 m*M* potassium phosphate, pH 3 and 60 m*M* C.S.	[150]
Fenoprofen, ibuprofen, ketoprofen	CZE	TM-β-CD	20 m*M* phosphate–20 m*M* triethanolamine, pH 5 and 25 m*M* C.S.	[99]
Herbicides (dichlorprop, fenoprop, mecoprop)	CE-MS	TM-β-CD	50 m*M* ammonium acetate, pH 4.6 and 20 m*M* C.S.	[156]
Ibuprofen, ketoprofen, naproxen, warfarin	CZE	TM-β-CD	0.1 *M* phosphate, pH 4.92, 0.1% HPMC and 8–15 m*M* C.S.	[61]

(*Continued on next page*)

Table 2 (*continued*)

Compounds	CE type	CD	BGE	Ref.
Imazamethabenz	CZE	TM-β-CD	50 m*M* sodium acetate, pH 4.6 and 10 m*M* C.S.	[192]
Mandelic acid	CZE	TM-β-CD	50 m*M* phosphate, pH 4 and 120 m*M* C.S.	[50]
Mexiletine	CZE	TM-β-CD	40 m*M* Tris–phosphoric acid, pH 2.5 and 20 m*M* C.S.	[102]
Non-steroidal antiinflammatory drugs (flurbiprofen, ibuprofen, ketoprofen, suprofen)	CZE	TM-β-CD	50 m*M* phosphate, pH 6 and 20–80 m*M* C.S.	[50]
p-Chlorowarfarin	CZE	TM-β-CD	50 m*M* phosphate, pH 6 and 40 m*M* C.S.	[50]
2-Phenylbutyric acid	CZE	TM-β-CD	50 m*M* phosphate, pH 5 and 10 m*M* C.S.	[50]
3-Phenylbutyric acid	CZE	TM-β-CD	50 m*M* phosphate, pH 5 and 40 m*M* C.S.	[50]
2-Phenyllactic acid	CZE	TM-β-CD	50 m*M* phosphate, pH 4 and 40 m*M* C.S.	[50]
2-Phenoxypropionic acid	CZE	TM-β-CD	50 m*M* phosphate, pH 4 and 10 m*M* C.S.	[50]
Tropic acid	CZE	TM-β-CD	50 m*M* phosphate, pH 5 and 20 m*M* C.S.	[50]
Warfarin	CZE	TM-β-CD	50 m*M* phosphate, pH 6 and 5 m*M* C.S.	[50]
Cyclodrine, cyclopentolate, norpseudoephedrine, phendimetrazine, pholedrine, terbutaline, mandelic acid, *p*-Br-mandelic acid, tropic acid	CZE	TMA-β-CD	50 m*M* acetate, pH 5 and 5–40 m*M* C.S.	[226]
N-Methylphenobarbital, hexobarbital, benzoin, 5-methyl-5-phenylhydantoin, thalidomide	CZE	TMA-β-CD	50 m*M* phosphate buffer, pH 3 and 5–25 mg/ml C.S.	[227]
1-Aminoindan, *cis*-1-amino-2-indanol, 1,2,3,4-tetrahydronaphthylamine	CZE	α-CD–30 m*M* 18-crown-6	50 m*M* sodium dihydrogenphosphate, pH 2.2 and 30 m*M* C.S.	[144]
Monoterpenes (α-pinene, β-pinene)	CZE	α-CD and Su-β-CD	10 m*M* phosphate, pH 3.3 and 1–6.5 m*M* C.S.	[228]
2-Amino-1,2-diphenylethanol, 1-aminoindan, *cis*-1-amino-2-indanol, 2-amino-3-phenyl-1-propanol, 3-amino-3-phenyl-propionic acid, blacofen, 4-chlorophenylalanine ethyl ester, 4-chlorophenylalanine methyl ester, DOPA, α-methylbenzylamine, 3-(1-naphthyl)alanine, 3-(2-naphthyl)alanine, 1-(1-naphthyl)ethylamine, *p*-nitrophenylalanine phenylalanine, theo-3-phenylserine, 1,2,3,4-tetrahydronaphthylamine	CZE	β-CD–30 m*M* 18-crown-6	50 m*M* sodium dihydrogenphosphate, pH 2.2 and 30 m*M* C.S.	[144]
Amino acids derivatives, dansyl (glutamic, aspartic acid)	CZE	β-CD-EA	50 m*M* NaH_2PO_4, pH 6 and 3 m*M* C.S.	[103]
Non-steroidal antiinflammatory drugs (fenoprofen, flurbiprofen, ibuprofen)	CZE	β-CD-EA	50 m*M* NaH_2PO_4, pH 4–7 and 1–5 m*M* C.S.	[103]
Phenoxypropionic acids	CZE	β-CD-EA	50 m*M* NaH_2PO_4, pH 5–8 and 20 m*M* C.S.	[103]
1-Methyl-3-phenylpropylamine	CZE	γ-CD and 18-crown-6 (10 m*M*)	100 m*M* phosphate, pH 2 and 10 m*M* CD	[142]
1-Aminoindan	CZE	γ-CD and 18-crown-6 (10 m*M*)	100 m*M* phosphate, pH 2 and 10 m*M* CD	[142]
1,2,3,4-Tetrahydro-1-naphthylamine	CZE	γ-CD and 18-crown-6 (10 m*M*)	100 m*M* phosphate, pH 2 and 10 m*M* CD	[142]
2-Amino-9-hydroxyfluorene, 1-aminoindan, *cis*-1-amino-2-indanol, 3-amino-3-phenyl-propionic acid, 4-chlorophenylalanine ethyl ester, 4-chlorophenilalanine methyl ester, α-methyltryptamine, α-methyl-*p*-tyrosine, 1-(1-naphthyl)ethylamine, *trans*-2-phenylcyclopropylamine-1,2,3,4-tetrahydronaphthylamine, tryptophan butyl ester	CZE	γ-CD–30 m*M* 18-crown-6	50 m*M* sodium dihydrogenphosphate, pH 2.2 and 30 m*M* C.S.	[144]
Quinolone drugs (ofloxacin, DX-9491-DV-7751, DU-6858-DU-6959)	CZE	γ-CD–Zn(II)-(L or D)-Phe	10 m*M* ammonium acetate, pH 6.5 and 5–20 m*M* C.S.	[229]

phoric acid–triethanolamine, pH 3). At the operating conditions the analyte was mainly uncharged and thus the use of a charged CD (SBE- or CM-β-CD) together with TM-β-CD allowed to obtain the optimum chiral resolution of *R,S*-naproxen. Good results with respect to linearity, precision were reported demonstrating the possibility to analyse 0.1–2% of *R*-naproxen as the enantiomeric impurity [236].

Ketoprofen enantiomers were determined in commercially available pharmaceutical formulations by CE using a phosphate–triethanolamine buffer at pH 5 supported with TM-β-CD. The LOD as low as $7 \cdot 10^{-7}$ *M* was observed and the *R*-(−)-ketoprofen [the impurity in the sample containing *S*-(+)-enantiomer] was determined by using the standard addition method. The authors found that the sample contained an enantiomeric excess of 99.54% (very similar to that found by HPLC) [237].

A method for the enantiomeric purity control of the pharmacological active (−)-terbutaline was optimised using different CDs dissolved in the BGE containing a removable liquid polyethylene glycol gel. The best resolution was achieved using 10 m*M* of HP-β-CD and 10% polyethylene glycol-2000 solution at 15°C. 0.1% of distomer/eutomer was detected [104].

The chiral resolution of the analgesic cizolirtine was reported by Torrens et al. [234] by CE using HP-β-CD dissolved into the buffer at pH 2.5. The optimised method was tested for the chiral purity control of the drug after the chiral separation by crystallisation with a chiral reagent. The results achieved in CE were compared with those obtained by NMR and HPLC.

7.2. Biological and medical analysis

The analysis of cicletanine enantiomers, used as the antihypertensive drug, was achieved by CE after extraction with diethyl ether from human plasma. Good detection limit (10 ng/ml for each enantiomer) and good linearity (10–500 ng/ml) were observed. The *S*-(+)-cicletanine isomer was found to be present in the plasma samples of two patients undergoing the therapy while urine samples contained only the *R*-(−)-enantiomer [126].

The potentiality of chiral capillary electrophoresis was demonstrated by Desiderio et al. studying the enantiomers separation of mephenytoin, phenytoin and their metabolites (4-hydroxy derivatives). The chiral separation was achieved using CD-modified MEKC employing the BGE at pH 9.1 containing 100 m*M* of sodium dodecyl sulphate, 50 m*M* of β-CD and 10% (v/v) of 2-propanol. The optimised method was applied for monitoring the enantiotransformation of mephenytoin and phenytoin in patients under therapy analysing urine samples. According to literature data, urine samples of extensive metabolisers revealed the presence of only *S*-4-hydroxymephenytoin while in the samples of poor metabolisers the presence of the hydroxymephenytoin derivatives was not found [127]. Okafo et al. also analysed mephenytoin and 4-hydroxymephenytoin using CD-MEKC with the addition of taurodeoxycholic acid (a chiral surfactant). The method was successfully applied for the analysis of a biological extract treated with hepatic microsomes [238].

Heuermann and Blaschke applied CZE using HP-β-CD as the chiral selector for the analysis of basic drug enantiomers, namely dimethindene and its metabolite *N*-demethyl-dimethindene in human urine. The validation was studied obtaining good results concerning sensitivity (1–2 ng/ml) [239].

The same group analysed clenbuterol enantiomers in human urine [240] after liquid–liquid extraction using a buffer at pH 3.3 supported with HE-β-CD. Detection limits as low as 0.5 ng/ml were observed and the biotransformation of the drug was stereoselective [the (+)-isomer was predominant in the urine sample].

Two different separation methods were optimised by Lerch and Blaschke for the enantiomeric separation of praziquantel and its metabolites (*trans*-4-hydroxy and *cis*-4-hydroxypranziquantel) using a negatively charged CD (SBE-β-CD). The optimised method was applied to the analysis enantiomeric drug after incubation with rat liver microcosms. The results obtained by CE were compared with those achieved by HPLC–MS [241].

CE using β-CD added to a phosphate buffer at pH 2.5 analysed amphetamine-related enantiomers, the main component of ''ecstasy''. Good sensitivity (0.2 μg/ml), precision and linearity were recorded and the method was applied for the analysis of urine and hair samples after liquid–liquid extraction [242].

An alternative method to previously described HPLC method for the analysis of minaserin and its metabolite in plasma was proposed by Eap et al. [243]. The separation of six couple of enantiomers was achieved using a phosphate buffer at pH 3 supplemented with a low concentration of HP-β-CD (2.5 m*M*). Sensitivity as low as nanogram level was achieved using on-column sample preconcentration after liquid–liquid extraction.

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one (ondansetron) is a selective 5-hydroxytryptamine-receptor antagonist used in the treatment of chemotherapy. The racemic drug was separated in its enantiomers using DM-β-CD added to the buffer at acidic pH. Serum samples containing *R* and *S* enantiomers were analysed after solid-phase extraction obtaining good results (linearity, sensitivity and precision) [244].

Ibuprofen and its major phase I metabolites (2′-hydroxyibuprofen and 2′-carboxyibuprofen) enantiomers in urine samples were separated by CE using TM-β-CD and dextrin 10. The presence of only *S*-ibuprofen, *S*-hydroxyibuprofen and two peaks of 2′-carboxyibuprofen was found in urine sample after intake of tablets containing *S*-ibuprofen [245].

The stereoselective separation of pentobarbital enantiomers from serum was obtained by CE using HP-γ-CD as the chiral selector [246] dissolved in a BGE at pH 9. Solid-phase extraction was done using a C_{18} Bond-Elut cartridge. Good precision, accuracy, detection and quantitation limits were demonstrated. The same group applied the CE method to the analysis of secobarbital in serum [247].

Kurth and Blaschke analysed tramadol and its main metabolites in urine samples by CE. A borate buffer at pH 10.6 allowed the baseline separation of tramadol and phase I and II metabolites while the simultaneous separation of tramadol and phase I metabolite enantiomers was achieved adding CM-β-CD to the BGE at basic pH. The optimised method was applied to human urine analysis after preconcentration (liquid–liquid) [248]. Tramadol and its main phase I metabolites in urine were also analysed by us using CM-β-CD dissolved in a BGE at pH 2.5 [249]. The method was validated and used for the urine analysis finding that a stereoselective metabolism of tramadol clearly occurred, this is shown in Fig. 6.

Zaugg et al. [250] used HP-γ-CD dissolved in a phosphate buffer at pH 8.5 for the separation of thiopental and its metabolite (pentobarbital). The optimised method was used for the analysis of the two couple of enantiomers in plasma extracts. The authors found a higher total plasma concentrations of *S*-(−)-thiopental and *R*-(+)-pentobarbital compared to *R*-(+)-thiopental and *S*-(−)-pentobarbital.

On line coupled capillary ITP and CZE was employed by Dankova et al. [251] for the analysis of L-(−)-tryptophan in urine. The resolution of the two standard enantiomers was achieved also when their concentration ratio was 1:200 while L-enantiomer concentration was 25 nmol/l. The LODs for the enantiomers were 1.5 ng/ml. 99% of anionic constituents in a real sample of urine, migrating in the on-line coupling ITP, were removed allowing an excellent clean-up and the determination of L-tryptophan. Fig. 7A and B show the ITP–CZE analysis of L-(−)-Trp without and with clean-up treatment, respectively.

7.3. Forensic analysis

Basic drugs of forensic interest were studied and separated in their enantiomers [253] employing a BGE with 10% (v/v) of methanol at pH 2.45 supported with 5 m*M* of DM-β-CD. Khat leave samples were analysed using the optimised method and (−)-cathinone, (+)-norpseudoepehedrine and small amount of (−)-norephedrine were found. The combination of DM-β-CD and sulphobutyl(VI)ether-β-CD (SBE-β-CD), a charged chiral selector, allowed the enantiomers resolution of amphetamine, methamphetamine and methcathinone. The authors showed that CE analysis using CDs can be an excellent tool in order to verify the unusually enantiomeric ratio in real samples of forensic interest. In fact cocaine should contain only the (−)-antipode and therefore finding either the (+)-isomer or the racemic mixture it can be proved that the drug comes from illicit synthesis.

7.4. Miscellaneous

HP-β-CD was used for the chiral resolution of D,L-pantothenic acid. After method optimisation 60 m*M* of CD added to a phosphate buffer at pH 7 modified with 10% of methanol allowed to obtain

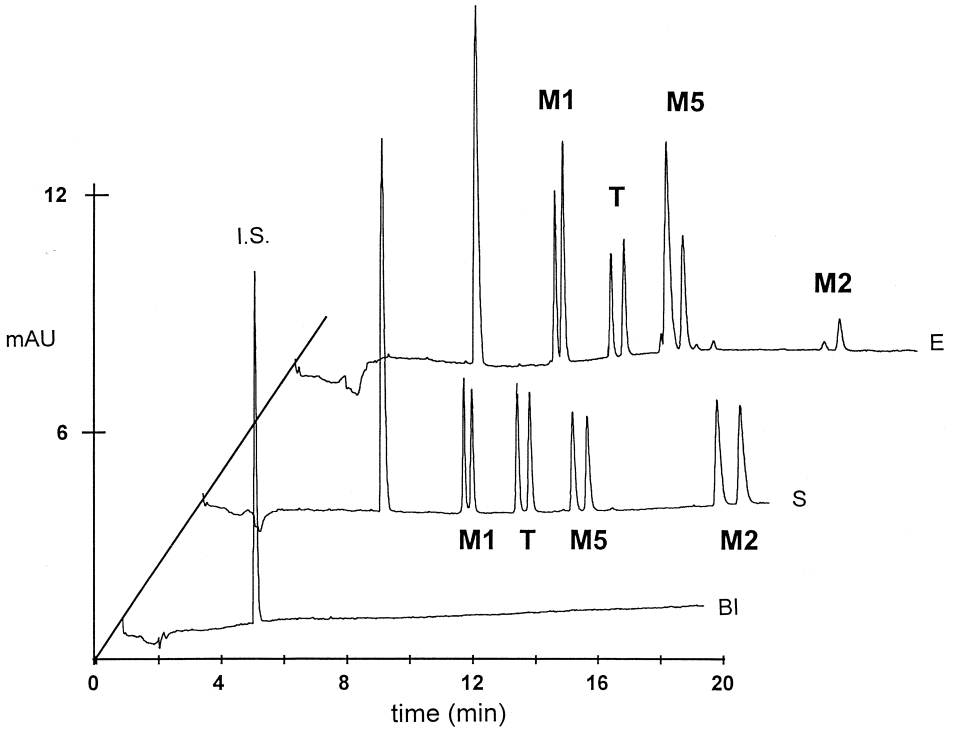


Fig. 6. Electropherograms obtained after liquid–liquid extraction of a blank urine spiked with (+)-ephedrine as internal standard (Bl), blank urine spiked with 2.5 μg/ml of each enantiomer of tramadol (T) and its main phase I metabolites (S) and a healthy volunteer urine sample collected during 6–8 h after an administered dose of 100 mg of tramadol (E). Background electrolyte, 50 m*M* phosphate buffer, pH 2.5 and 5 m*M* CM-β-CD (modified from Ref. [249]).

enantiomers baseline separation. Besides good linearity, repeatability and recovery were demonstrated, a detection limit as low as 3% of L-isomer was observed. The method was applied to the analysis of D,L-pantothenic acid in soft drinks finding only the D-isomer [262].

Our group analysing a commercial formulation of flamprop isopropyl herbicide containing only the *R*-isomer also demonstrated the actual applicability of CE to the stereoselective analysis of samples of environmental interest. Here SBE-β-CD served as chiral resolving agent as well as the transporting compound inducing the charge to the analytes [211]. Recently an interesting paper by Marina and Crego [265] reviewed the chiral separation achieved by using CE.

Applications in environmental field was also demonstrated by Kanz et al. [261] studying the biodegradation of linear alkylbenzenesulphonates enantiomers by CE using α-CD as the chiral selector. A detection limit as low as 1 μg/l was achieved.

The chiral purity control of *S*- or *R*-camphorsulphonic acid (commercially available) was performed by Tanaka et al. [154] using CE–MS. The authors found the presence 0f 2 and 0.9% of *S*- and *R*-form, in the samples declared to contain *R*- and *S*-enantiomer, respectively.

Table 3 reports a list of the main application of chiral CE analysis to real samples.

8. Conclusions

Using CE with CDs as chiral selector enantioselective determinations can easily be performed. The analysis can be carried out simply adding to the BGE the chiral selector that can be selected among the wide range, either charged or uncharged, com-

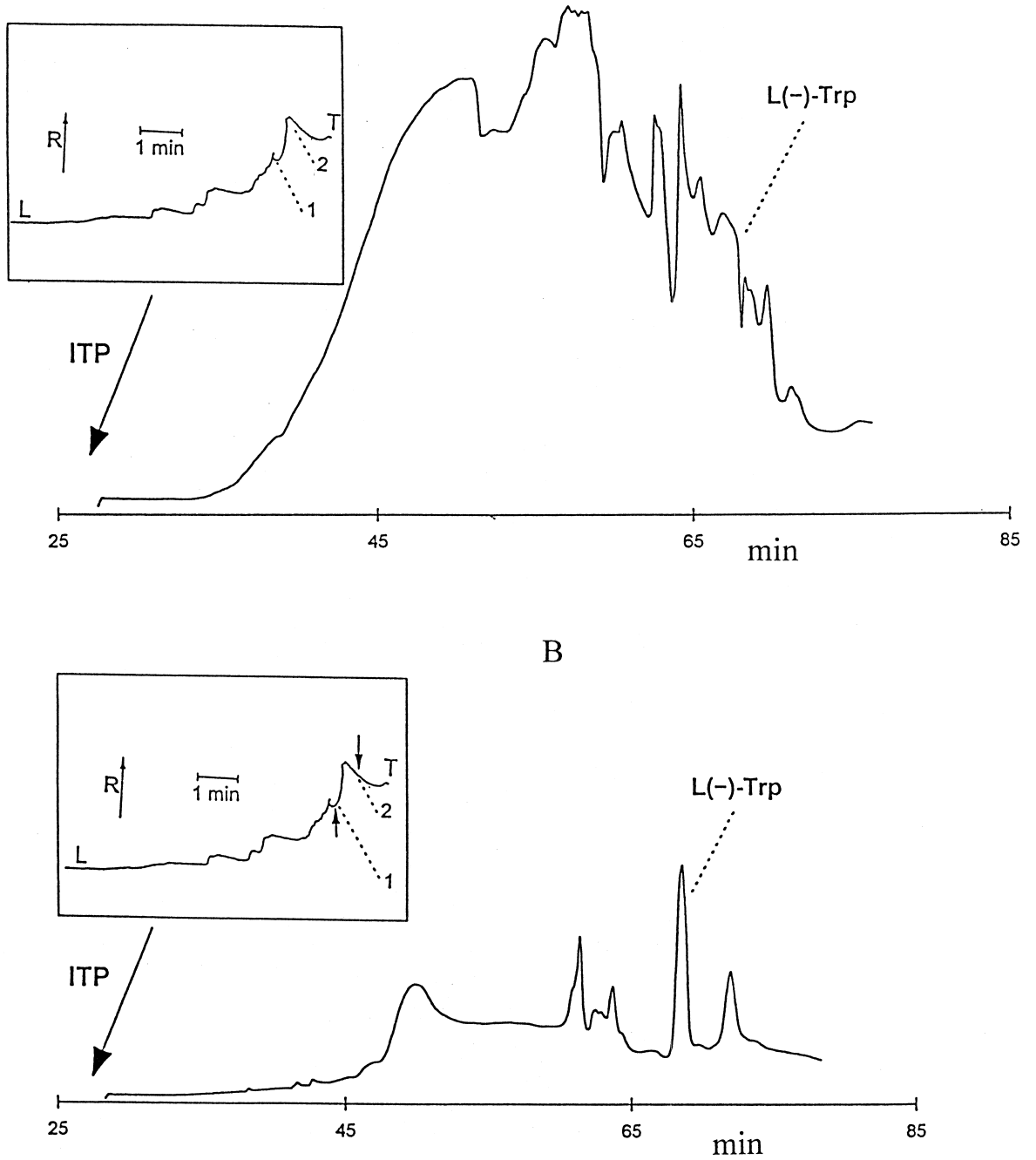


Fig. 7. ITP–CZE analysis of L-tryptophan in human urine (A) without and (B) cutting the interfering zones (modified from Ref. [251]).

mercially available. Furthermore excellent results can be also obtained employing CDs bound to the capillary wall (electrochromatography).

CDs are the most popular chiral selectors used in CE probably due to their properties, e.g., good solubility in aqueous solvents, very low absorption at

Table 3
The main applications

Compounds	Sample	CE type	Chiral selector	BGE	Ref.
Amphetamine, methamphetamine	Urine	CZE	HP-β-CD	100 m*M* Tris–phosphate, pH 2.5 and 20 m*M* C.S.	[252]
Atropine	Serum	CZE	TM-β-CD	50 m*M* Tris–phosphate, pH 2.8 and 40 m*M* C.S.	[225]
Camphorsulphonic acid	Commercial	CE–MS	DM-β-CD	40 m*M* ammonium formate, pH 4 and 50 m*M* C.S.	[154]
(−)-Cathinone, (−)-norephedrine, (−)-norpseudoephedrine	chemical Khat leaves	CZE	DM-β-CD	90% (25 m*M* Tris–H_3PO_4, pH 2.45 and 5 m*M* C.S.) and 10% methanol	[253]
Cicletanine	Plasma	CD-MEKC	γ-CD	100 m*M* sodium borate, pH 8.6, 110 m*M* SDS, 10% acetonitrile and 25 m*M* C.S.	[126]
Cizolirtine	Drugs	CZE	HP-β-CD	100 m*M* phosphate, pH 2.5 and 25 m*M* C.S.	[234]
Clenbuterol	Urine	CZE	DM-β-CD	50 m*M* borax–H_3PO_4, pH 2.5 and 16 m*M* C.S.	[254]
Clenbuterol	Urine	CZE	HE-β-CD	200 m*M* phosphate buffer, pH 3.3 and 30 m*M* of C.S.	[240]
Dexchlorpheniramine	Drugs	CZE	β-CD and CM-β-CD	phosphate buffer, pH 3.5 and	[235]
Dextrometorphan dextrophan levorphanol	Urine	MEKC	β-CD	80% 50 m*M* sodium tetraborate, 50 m*M* HCl, 50 m*M* SDS, pH 9.05 and 60 m*M* C.S–20% 1-propanol	[255]
Dimethindene-*N*-dimethyl-dimethindene	Urine	CZE	HP-β-CD (molar substitution, MS=0.9)	100 m*M*; run: 50 m*M* phosphate buffer, pH 3.3 and 30 m*M* C.S.	[239]
Doxylamine	Cough syrup	CZE	CM-β-CD	20 m*M* citric acid, pH 2.5 and 4% C.S.	[256]
Ephedrine	Cough syrup	CZE	CM-β-CD	20 m*M* citric acid, pH 2.5 and 4% C.S.	[256]
Ephedrines [(−)-ephedrine, (+)-pseudoephedrine, (−)-*N*-methylephedrine, (−)-norephedrine]	Plant extracts	CZE–MEKC	HP-β-CD	30 m*M* Tris–H_3PO_4 and 30 m*M* HP-β-CD, 30 m*M* TMAC and 10 m*M* SDS	[257]
Epinephrine	Drug	CZE	DM-β-CD	50 m*M* Tris–phosphate, pH 2.5 and 20 m*M* C.S.	[230]
			DM-β-CD	10 m*M* Tris–H_3PO_4, pH 2.4 and 18 m*M* C.S.	[231]
m-Fenfluramine	Drug	CZE	TM-β-CD	100 m*M* H_3PO_4–Tris, pH 2.5 and 40 m*M* C.S.	[232]
Flamprop isopropyl herbicide	Herbicide formulation	CZE	SBE-β-CD	20 m*M* borate, pH 9 and 80 mg/ml C.S.	[211]
Flezelastine *N*-dephenethylflezelastine	In vitro	CZE	β-CD	100 m*M* phosphate, pH 3.75	[258]
Haloperidol and metabolite	Plasma	CZE	DM-β-CD	40 m*M* Tris–phosphate buffer, pH 2.5, 20 mg/ml PEG 6000 and 10 m*M* C.S.	[259]
Hexobarbital	Rat plasma	MEKC	β-CD	20 m*M* phosphate buffer, pH 7, 100 m*M* SDS and 30 m*M* C.S. and 15% MeOH	[89]
Ibuprofen	Serum	CZE	Maltrin M040	30 m*M* TAPS, 10 m*M* Tris, pH 7.8, 5% C.S.	[260]
Ibuprofen, 2′-hydroxyibuprofen, 2′-carboxyibuprofen	Urine	CZE	TM-β-CD–dextrin 10	100 m*M* MES, pH 5.26, 0.01% HDB, 20 and 10 m*M* C.S.	[245]
Ketoprofen	Pharmaceutical	CZE	TM-β-CD	20 m*M* phosphate–20 m*M* triethanolamine, pH 5 and 50 m*M* C.S.	[237]
Leucovorin-5-methyl-tetrahydrofolate	Plasma	CZE	γ-CD	Sodium phosphate buffer, pH 9, *I*=0.3, 0.2 *M* C.S., 6 *M* urea	[107]

(*Continued on next page*)

Table 3 (*continued*)

Compounds	Sample	CE type	Chiral selector	BGE	Ref.
Mephenytoin-4-hydroxy-mephenytoin	Urine	CD-MEKC	β-CD+TDOC	30 m*M* NaH_2PO_4, 10 m*M* boric acid, pH 7.2, 20 m*M* CD and 50 m*M* TDOC, 5.6 m*M* sodium tetraborate and 8.4 disodium hydrogenphosphate,	[238]
	Urine	CD-MEKC	β-CD	pH 9.1 and 95 m*M* SDS, 40 m*M* C.S., 8% (v/v) 2-propanol	[127]
3,4-Methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyethylamphetamine (MDE)	Hair	CZE	β-CD	100 m*M* phosphate buffer, pH 2.5 and 15 m*M* of C.S.	[242]
Mianserine and its metabolites (desmethylmianserine, 8-hydroxymianserin	Plasma	CZE	HP-β-CD	H_3PO_4–triethylamine, pH 3 and 2.5 m*M* C.S.	[243]
Naproxen	Drugs	CZE	SBE-β-CD–TM-β-CD	100 m*M* phosphoric acid–triethanolamine, pH 3 and 5 m*M*–20 m*M* C.S.	[236]
p-Sulphophenyl-2-butyrate, *p*-sulphophenyl-3-butyrate	Sewage effluent	CZE	α-CD	20 m*M* citrate, pH 4 and 60 m*M* C.S.	[261]
Ondansetron	Serum	CZE	DM-β-CD	100 m*M* sodium dihydrogenphosphate, pH 2.3–0.03 m*M* HTAB and 15 m*M* C.S.	[244]
Pantothenic acid	Soft drinks	CZE	HP-β-CD	60 m*M* phosphate buffer, pH 7–10% MeOH and 60 m*M* of C.S.	[262]
Pentobarbital	Serum	CZE	HP-γ-CD	50 m*M* phosphate, pH 9 and 40 m*M* C.S.	[246]
Praziquantel, *trans*-4-hydroxypraziquante, *cis*-4-hydroxypraziquantel	Incubation rat liver microsomes	CZE	SBE-β-CD	50 m*M* phosphate, pH 5.25 and 4 m*M* C.S.	[241]
Prilocaine	Serum	CZE	DM-β-CD	100 m*M* phosphate, pH 2.5, 0.03 m*M* HTBA and 15 m*M* C.S.	[263]
Secobarbital	Serum	CZE	HP-γ-CD	50 m*M* phosphate, pH 9 and 40 m*M* C.S.	[247]
Tamoxifen	Drugs	CZE	β-CD	50 m*M* phosphate, pH 7–50 m*M* borate, pH 9.3–methanol (40:10:50) and saturated C.S.	[233]
Thiopental	Serum	CZE	HP-γ-CD	75 m*M* phosphate, pH 8.5 and 5 m*M* C.S.	[250]
Tramadol and metabolites	Urine	CZE	CM-β-CD	50 m*M* borate, pH 10.2 and 20 mg/ml C.S.	[248]
Tramadol and metabolites	Urine	CZE	CM-β-CD	50 m*M* phosphate buffer, pH 2.5 and 5 m*M* of C.S.	[249]
Trimetoquinol	Drug	CZE	EP-β-CD	25 m*M* phosphate buffer, pH 2.7 and 5% β-CD polymer	[28]
Tryptophan	Urine	ITP–CZE	α-CD	ITP: LE, 10 m*M* chloride–BTP, 0.2% MHEC, pH 9.3; TE, 10 m*M* borate–BTP, pH 10 CZE: 50 m*M* borate, 0.2% MHEC, pH 9.0 and 80 m*M* C.S.	[251]
Verapamil, norverapamil	Plasma	CZE	TM-β-CD	60 m*M* phosphate, pH 2.5 and 60 m*M* C.S.	[264]
Warfarin	Serum	CZE	Glucidex 2	10 m*M* Tris–phosphate, pH 7 and 2.5% C.S.	[28]
				100 m*M* sodium phosphate buffer, pH 8.35, 8 m*M* C.S.–MeOH (98:2, v/v)	
	Plasma	CZE	DM-β-CD (degree of substitution 1.8)		[90]

the used wavelengths, wide selection of commercial compounds, etc. Powerful chiral CE analysis can be carried out selecting the appropriate experimental conditions, e.g., CD type and concentration, buffer composition (pH, ionic strength and organic modifier) etc. The method is rapid and not expensive because minute amounts of BGE containing CDs are employed. Besides the wide number of enantiomers resolved by CE, only a reduced number of applications are available in literature.

Finally it is noteworthy to mention that the applicability of CDs for preparative CE chiral separations was recently shown by several authors [266–269]. The potential of classical preparative chiral gel electrophoresis employing a sulphated-β-CD for the preparation of milligrams of chiral terbutaline was demonstrated by Stalcup et al. [266]. Hoffmann et al. purified (*R*)-(−)-methadone on a mg/h scale by chiral continuous flow ITP with HP-β-CD as the chiral selector [267]. Glukhovskiy and Vigh used preparative IEF for the separation of L- and D-dansyl phenylalanine, obtaining a production rate of 1.33 mg/h and an enantiomeric excess better than 99.99% [268]. Recently ITP, operating in a discontinuous fractionation mode, was used for the separation 2,4-dinitrophenyl-norleucine enantiomers adding to the leading electrolyte β-CD (each preparative run provided up to 14 μg of pure enantiomers [269]).

9. Abbreviations

2,3-Dac-β-CD	Heptakis(2,3-di-*O*-acetyl)-β-cyclodextrin
2,6- or 3,6-DM-γ-CD	2,6- or 3,6-di-*O*-methyl-γ-cyclodextrin
18-crown-6-ether	18-crown-6-ether
AM-β-CD	Amphoteric-β-cyclodextrin
APOC	1-(9-anthryl)-2-propyl chloroformate
AQC	6-aminoquinolyl-*N*-hydroxysuccinimidyl carbamate
β-CD-CN	Cyanoethylated-β-CD
β-CD-EA	Heptakis(6-hydroxyethylamino-6-deoxy-β-cyclodextrin)
β-CD-Glu	Mono-(6-δ-glutamylamino-6-deoxy)-β-cyclodextrin
BDCA	1,1′-binaphthyl-2,2′-dicarboxylic acid
BDHP	1,1′-binaphthyl-2,2′-dihylhydrogenophosphate
BGE	Background electrolyte
BTP	1,3-bis-[tris(hydroxymethyl)-methylamino]propane
CD	Cyclodextrin
CD-MEKC	Cyclodextrin-modified micellar electrochromatography
CE	Capillary electrophoresis
CE-β-CD	Carboxyethylated-β-cyclodextrin
CEC	Capillary electrochromatography
CE-MS	Capillary electrophoresis coupled to mass spectrometry
CGE	Capillary gel electrophoresis
CM-β-CD	Carboxymethylated-β-cyclodextrin
C.S.	Chiral selector
CZE	Capillary zone electrophoresis
DM-β-CD	Heptakis(2,6-di-*O*-methyl)-β-cyclodextrin
EOF	Electroosmotic flow
EP-β-CD	β-cyclodextrin polymer
EtCa-β-CD	Ethylcarbonate-β-cyclodextrin
EtNH-β-CD	Ethylamino-β-cyclodextrin
FLEC	1-(9-Fluorenyl)ethyl chloroformate
FMOC	9-Fluorenylmethyl chloroformate
HDB	Hexadimethrine
HDAS-β-CD	Heptakis-(2,3-diacetyl-6-sulphato)-β-cyclodextrin
HDMS-β-CD	Heptakis-(2,3-dimethyl-6-sulphato)-β-cyclodextrin
HE-β-CD	Hydroxyethyl-β-cyclodextrin
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulphonic acid
HP-β-CD	2-hydroxypropyl-β-cyclodextrin
HP-γ-CD	Hydroxypropyl-γ-cyclodextrin
HPMC	Hydroxypropyl methyl cellulose
HS-β-CD	Hepta-6-sulphato-β-cyclodextrin
HTAB	Hexadecyltrimethylamonium bromide
HTAP-β-CD	2-Hydroxy-3-trimethylammoniumpropyl ether-β-cyclodextrin
IEF	Isoelectric focusing
ITP	Isotachophoresis

LE	Leading elecrolyte
MALDI-TOF	Matrix-assisted laser desorption ionisation time-of-flight
MeNH-β-CD	Methylamino-β-cyclodextrin
MES	2-(*N*-Morpholino)ethanesulphonic acid
MHEC	Methylhydroxyethylcellulose
NMR	Nuclear magnetic resonance
NSAIDs	Non-steroidal antiinflammatory drugs
OTCEC	Open tubular electrochromatography
PEG	Poly(ethylene glycol)
Phos-β-CD	Phosphated-β-cyclodextrin
PM-β-CD	Permethylated-β-cyclodextrin modified silica support
PPAHs	Phenoxypropionic acid herbicides
PTH	Phenylthiohydantoin
QA-β-CD	Quaternary ammonium-β-cyclodextrin
SBE-β-CD	Sulphobutyl(IV)ether-β-cyclodextrin
SDS	Sodium dodecyl sulphate
SPE-β-CD	Sulpho-*n*-propyl ether-β-cyclodextrin
Su-β-CD	Sulphated-β-cyclodextrin
SUC-β-CD	Succynil-β-cyclodextrin
TAPS	*N*-Tris(hydroxymethyl)-methyl-3-aminopropane sulphonate
TBA	Tetrabutylammonium bromide
TDOC	Taurodeoxycholic acid
TMA	Tetramethylammonium
TMAC	Tetramethylammonium chloride
TM-β-CD	Heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin
TMA-β-CD	2-Hydroxy-3-trimethylammoniopropyl-β-cyclodextrin
TPA	Tetrapropylammonium
Tris	Tris(hydroxymethyl)aminomethane

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