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Recent chiral selectors for separation in HPLC and CE

Review Article

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Abstract: Enantiomers (stereoisomers) can exhibit substantially different properties if present in chiral environments. Since chirality is a basic property of nature, the different behaviors of the individual enantiomers must be carefully studied and properly treated. Therefore, enantioselective separations are a very important part of separation science.

To achieve the separation of enantiomers, an enantioselective environment must be created by the addition of a chiral selector to the separation system. Many chiral selectors have been designed and used in various fields, such as the analyses of drugs, food constituents and agrochemicals. The most popular have become the chiral selectors and/or chiral stationary phases that are of general use, *i.e.*, are applicable in various separation systems and allow for chiral separation of structurally different compounds.

This review covers the most important chiral selectors / chiral stationary phases described and applied in high performance liquid chromatography and capillary electrophoresis during the period of the last three years (2008-2011).

Keywords: *High performance liquid chromatography • Capillary electrophoresis • Chiral selector • Chiral stationary phase • Enantioselective separation*

1. Introduction

Many reviews dealing with enantioselective separations have been published over the last few years. Based on the topic they focused on, the reviews can be roughly categorized as reviews on various chiral selectors (CSs) or chiral stationary phases (CSPs), on enantioselective separation mechanism, and application. Often it is a combination of these topics. Some reviews are published annually, some every two or three years. These papers are mostly entitled "fundamental" reviews but other papers, also fundamental, appear in the literature, as well.

As we do not wish to repeat the information which has been already reviewed, and considering the tremendous number of papers covering the topic, we decided to focus on papers that have not been reviewed previously, *i.e.*, published between January 2010 and May 2011. The reviews published between January 2008 and May 2011 (according Web of Science) are summarized in Table 1 (liquid chromatography) and Table 2 (capillary electrophoresis). Basic research papers contribute to the explanation of chiral recognition mechanism and analytical applications are of interest to analysts from commercial laboratories. Therefore, we have included both aspects in this review.

As CSPs play the most important role in chiral high performance liquid chromatography (HPLC) separations, the HPLC part of this review has been divided into subchapters based on the various CS/CSP types used. In addition, different separation modes that can be used are discussed.

The capillary electrophoresis (CE) is more difficult to categorize. The variety of chiral selectors, as well as the different electromigration methods, such as capillary zone electrophoresis (CZE), micellar electrokinetic chromatography (MEKC) or capillary electrochromatoghraphy (CEC) can be used and contribute to diverse separation mechanisms.

2. HPLC

Table 1 summarizes the recent reviews relating to chiral HPLC separations using different chiral stationary phases.

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Table 1. An overview of the review articles dealing with enantioselective separation in HPLC published in the period between January 2008 and May 2011.

CS/CSP*	Topic	Analytes	Ref.
	LEC, CZE and CEC		[1,2]
	preparation of new CSPs by click chemistry, application		[3]
polymeric, macrocyclic, brush type, ligand exchange CSPs	silica-based CSPs		[4]
	development of new CSPs, application		[5]
major commercially available CSPs	application	active pharmaceutical ingredients	[6]
	application	pharmaceuticals	[7]
	application	organophosphorus pesticides	[8]
	application	fluoroquinolones antibiotics	[9]
	application	biologically important small epimeric peptides and their amino acid components	[10]
	application	pyrethroids	[11]
	chiral modified silica monolithic columns		[12]
	monolithic CSPs, application		[13]
modern CS/CSPs	separation mechanism		[14]
	indirect LC, application	D,L-penicillamine	[15]
	application	pharmaceuticals in aquatic environment	[16]
macrocyclic glycopeptide-based CSPs	separation mechanism, physicochemical properties		[17]
polysaccharide derivatives	CSPs, application		[18]
tartrates and metal-tartrates CS	CS, application		[19]
coated/immobilized polysaccharide CSPs	CSPs, application	chiral pharmaceuticals	[20]
	application	antidepressant drugs and their metabolites in biological samples	[21]
	application	pesticides	[22]
	application	triptans	[23]
	application	amino acids in biological samples	[24]
	reversed CSPs, application	pharmaceutical compounds	[25]
Pirkle-type, polysaccharide-based CSPs	CSPs, application	pharmaceutical compounds	[26]
penicillin G acylase CS	CS		[27]
	ion-pair chromatography, application		[28]
	application	pharmaceutical formulations	[29]
vancomycin and its degradation products	CS, application		[30]
	CS/CSPs, application		[31]
macrocyclic antibiotics	recognition mechanism, application		[32]
	chiral separations since 1998 to 2008		[33]
protein/glycoprotein CSPs	recognition mechanism		[34]
chitosan phenyl carbamate derivatives	CSPs		[35]
	chiral and achiral methods, application	thalidomide and its metabolites	[36]
	application	adrenergic drugs	[37]
	CSPs, application		[38]
	CSPs		[39]
Chiralpak IA, Chiralpak IB, Chiralpak IC	application, methods compatible with MS		[40]
polysaccharide-, macrocyclic glycopeptide-, protein-, cyclodextrin-based CSPs	application, methods compatible with MS/MS	chiral drugs and/or their metabolites	[41]
	application	antimalarial drugs and their metabolites	[42]

**If the CSs/CSPs are not stated the review gives an overview of various types.*

2.1. Recent chiral HPLC

The majority of enantioselective HPLC systems are composed of a chiral stationary phase and an achiral mobile phase. This fact is reflected in this review.

2.1.1. Cyclodextrin-based CSPs

Cyclodextrin (CD) CSPs are still widely used in chiral and achiral HPLC as confirmed by the number of papers published since 2010. Commercially available or newly modified (derivatized with various groups) CD CSPs are remaining popular in both basic research and applications.

ChiraDex Beta (β-CD CSP) and ChiraDex Gamma (γ-CD CSP) columns were used for an achiral separation of 9,10-antraquinone derivatives in reversed phase (RP) mode with gradient elution [43]. An off-line two-dimensional reversed phase/reversed phase liquid chromatography (2-D RP/RPLC) method combining stationary phase C18 and β-CD CSP was developed for achiral separation of more than 500 components in extracts of *Fructus schisandrae chinensis*, which represent traditional Chinese medicine [44]. Two new CSPs were prepared by bonding mono[6-deoxy-(*R*)-(−)-N-1-(2-hydroxyl)-4-chlorophenylethylimino]-β-cyclodextrin (*R*-CPGCD) and mono[6-deoxy-(*R*)-(−)-N-1-(2-hydroxyl)-4-hydroxy-methylphenylacetate-imino]-β-cyclodextrin (*R*-HMPGCD) to silica gel, chiral nitro aromatic alcohol derivatives were separated on these CSPs in RP and polar organic (PO) modes [45]. Another novel CD-based CSPs containing mono(6(A)-N-(omega-alkenylamino)-6(A)-deoxy) perphenylcarbamoylated β-cyclodextrin with spacers of three different lengths were prepared, compared and applied for enantioseparation of various racemates in normal phase (NP) mode [46]. Four novel ionic liquids functionalized β-CDs CSPs were prepared and their enantioselectivities were tested with 16 chiral aromatic alcohol derivatives and 2 racemic drugs in PO mode [47]. Hydrobenzoin and structurally related compounds (benzoin and α-phenetyl alcohol) were successfully separated on β-CD and hydroxypropyl-β-cyclodextrin (HP-β-CD) in RP HPLC [48]. The new synthesized CD-based CSPs: heptakis(6-deoxy-6-azido)-β-CD and heptakis(6-deoxy-6-azido-phenylcarbamoylated) β-CD showed good enantioselectivity with over forty pairs of different enantiomers [49]. Another novel CD derivative, mono(6(A)-azido-6(A)-deoxy)-per(p-chlorophenyl carbamoylated) β-CD immobilized onto an amino-functionalized silica gel with different pore and particle sizes was examined by enantioseparation of variety of racemates in NP and RP modes [50]. A series of imino-modified β-CD derivatives were bonded to silica gel to form a new CD-based CSPs; their separation performance was examined with the separation of different compounds, *i.e.,* amino acids, chiral aromatic alcohol *etc.* [51]. A click chemistry strategy was used in the preparation of a new CD-based CSs and evaluated by chiral separation of various analytes, *i.e.,* aryl alcohols, flavonoids, atropine, β-blockers *etc.* [52]. A click chemistry-derived β-cyclodextrin (CD-click-sil and CD-click-RAM) CSPs were evaluated by enantioseparation of mandelic acid and chlorthalidone in human plasma [53], and a novel chiral-CD-RAM CSP prepared via atom transfer radical polymerization was tested on enantioseparation of some chiral drugs [54]. Newly prepared ethylenecliamine-β-cyclodextrin functionalized poly(glycidyl methacrylate-co-ethyleneglycol dimethacrylate) monoliths were characterized by scanning electron microscopy, differential scanning calorimetry and X-ray photoelectron spectroscopy and used for the chiral separation of racemic ibuprofen [55]. Two new types of substituted β-CD CSPs, which actually combined two powerful CSs (macrocyclic antibiotics and CD), vancomycin-capped β-CD-bonded silica particles and rifamycin-capped β-CD-bonded silica particles, were developed, characterized and tested with separation of achiral disubstituted benzenes and chiral drugs [56]. Bromine-containing β-CD-bonded stationary phase (BACD-HPS, bromoacetate-substituted [3-(2-O-β-CD)-2-hydroxypropoxy]propylsilyl-appended silica particles) were prepared and evaluated by separation of achiral disubstituted benzenes and some chiral drug compounds [57]. Native and derivatized CD CSPs (high performance hydroxypropylether-β-CD, hydroxypropylether-β-CD, acetylated β-CD, *R*- and *S*- naphthylethylcarbamate-β-CDs, dimethylphenylcarbamate-β-CD, 2,6-dinitro-4-trifluoromethylphenylether-β-CD, dimethylated β-CD) were chosen for enantioseparation of fifteen racemic 4,5-disubstituted imidazole compounds, and the mechanism of chiral recognition was discussed [58]. π-acidic and π-basic perphenylcarbamoylated β-CDs were synthesized and their enantioselectivities were examined and compared using a set of 2-piperazine-1,2-dihydronaphthaline derivatives and other chiral compounds in NP and RP modes [59]. Enantioseparation of a set of β-lactams was predicted and confirmed on three β-CD based CSPs, permethyl-β-CD, β-CD and *R,S*-HP-β-CD [60,61].

In addition to their excellent enantioseparation abilities CD CSPs show interesting capabilities for achiral application in hydrophilic interaction liquid chromatography (HILIC). Wang *et al.* carried out an achiral separation of a series of three cycloinulooligosaccharides (cyclofructans) on the Cyclobond I 2000 column (β-CD

CSP) in HILIC mode [62]. Cyclobond I 2000 (native β-CD CSP) and Cyclobond I 2000AC (acetylated β-CD CSP) columns exhibited great potential for achiral separation of estrogen and estrogen conjugated compounds in HILIC mode [63]. However, CD-based CSPs are mostly applied in RP separation mode or with PO mobile phase. Under these conditions they yield the best results.

Cyclodextrins were also used as mobile phase additives for chiral and achiral separations in HPLC [64-69]. However, this way of creating a separation environment is less popular than the use of CD-based stationary phases.

2.1.2. Polysaccharide CSPs

Recently, polysaccharide-based CSPs are the most frequently used group of CSPs used in chiral HPLC method development. Many studies reported during the review period discuss the enantiorecognition mechanism.

These CSPs are commercially available as either immobilized or coated on a support surface. The limited stability of coated CSPs could be a disadvantage as compared with CD CSPs that can resist repeatable changes among all known separation modes. The coated CSPs can be used with a rather limited number of eluents (alkane/alcohol mixtures) in NP chromatography and water/acetonitrile mixtures in RP chromatography. Solvents with intermediate polarities (*e.g.* ethyl acetate, tetrahydrofuran (THF), 1,4-dioxane, acetone) can partially or totally dissolve the chiral polymer. Chemically bonded (immobilized) polysaccharide CSPs have been developed to overcome the drawbacks of the coated CSPs and broaden the range of applicable solvents [70].

Immobilized Chiralpak IC, Chiralpak IA and coated Lux Cellulose-1, Lux Cellulose-2 and Lux Amylose-2 CSPs were used for the enantioseparation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline, all three separation modes (RP, NP and PO) were tested [71]. Chiral separation of eight racemic atropisomers of biphenyl was investigated on six polysaccharide CSPs in NP and PO modes [72]. Enantioselectivity of four recently commercialized CSPs, *i.e.,* Lux (R) Cellulose-1, Lux (R) Cellulose-2, Lux (R) Amylose-2 and Lux (R) Cellulose-4 were tested on a set of 61 racemic compounds in normal phase mode [73]. Preparative enantioseparation of substituted 4-oxo-1,4-dihydroquinoline-3-carboxamide derivatives (new potential selective agonists of the cannabinoid CB2 receptor) was performed on a Chiralpak AD-H column (amylose tris(3,5-dimethylphenylcarbamate) CSP) in NP mode [74]. Three chlorine containing cellulose-based CSPs, *i.e.,* cellulose tris(3-chloro-4-methylphenylcarbamate) (Sepapak-2s column), cellulose tris(4-chloro-3-methylphenylcarbamate) (Sepapak-4s column) and cellulose tris(3,5-dichlorophenylcarbamate) (Sepapak-5s) were evaluated by the separation of basic amino-drug enantiomers in PO mode [75]. Neonicotinoid insecticides were enantioseparated on Chiralcel OD-H, Chiralpak AD-H and Chiralpak IB columns in NP mode, but also using supercritical fluid chromatography (SFC) [76]. The types of interactions play a role in the mechanism of enantioselective recognition and the thermodynamic parameters affecting the process were discussed. Amylose tris(3,5-dimethylphenylcarbamate) CSPs was used for the enantioseparation of newly synthesized triazole fungicides in NP mode [77]. The 3,5-dimethylphenylcarbamate derivatized amylose and cellulose CSPs in systems with PO eluents were compared in terms of the enantioseparation of coumarin-based compounds [78]. The 2-D RP HPLC method using a C8 RAM BSA column as the first step followed by amylose tris(3,5-dimethoxyphenylcarbamate) CSP for the determination of lansoprazole in human plasma was developed and validated [79]. The enantioseparation of eight novel (*R,S*)-N-mexiletine derivatives with different alkyl chain lengths were performed on both a Chiralcel OD-H column and a Chiralcel OJ-H column under NP conditions [80]. Chiralpak IA and Chiralpak IC columns were used for the enantioseparation of new quinazoline derivatives bearing an α-aminophosphonate moiety under NP conditions; the chiral recognition mechanism was also discussed [81]. Chiralpak IA and Chiralpak IC columns were also applied to the enantioseparation of hypericin, pseudohypericin and protohypericin in PO mode; optimized HPLC conditions were used for determination of stereodynamic parameters of interconversion of the enantiomers [82]. HPLC methods were developed for the enantioseparation of five new aminonaphthol analogs in systems with amylose tris(3,5-dimethylphenylcarbamate) CSP (Kromasil ®AmyCoat ™ column) or cellulose tris(3,5-dimethylphenylcarbamate) CSP (Kromasil ® CelluCoat ™ column), the influence of the mobile phase composition on enantioseparation was tested [83]. Relative content of (2*S*)- and (2*R*)-naringin in the albedo of pummelo during maturation during the entire season was determined by a NP HPLC using Chiralpak IB column [84]. The enantioseparation of α-arylthiocarboxylic acids (*i.e.,* pirinixic acid derivatives) with different substitution patterns were performed on amylase tris(3,5-dimethylphenylcarbamate)-coated silica, tert-butylcarbamoylquinine CSPs and quinidine-based anion exchangers in analytical and preparative scale [85]. Fenoterol enantiomers were separated after precolumn fluorescence derivatization with naphthylisocyanate on cellulose tris(3,5-dimethylphenylcarbamate)-coated silica gel column

(OD-RH column) in RP mode [86]. More than 200 racemic compounds of pharmaceutical interest were used for the evaluation of three complementary three polysaccharide-based CSPs, *i.e.,* cellulose tris(3-chloro-4-methylphenylcarbamate), amylose tris(2-chloro-5-methylphenylcarbamate) and cellulose tris(3,5-dimethylphenylcarbamate) CSPs in RP mode compatible using mass spectrometry (MS) detection. Chiral separation in RP mode was compared with NP and PO modes [87]. Amylose tris(3,5-dimethylphenylcarbamate) CSP was used for the enantioseparation of racemic benzylmandelate. The retention behavior of the enantiomers were explained by nuclear magnetic resonance (NMR) experiments [88]. The enantiorecognition ability of cellulose tris(4-chloro-3-methylphenylcarbamate) coated CSP (Sepapak-4) was evaluated by the chiral separation of ten basic drugs of different structures and hydrophobicities using PO mobile phases [89]. Enantioseparation of 14 similar chiral solutes (with one or two chiral centers) were examined on amylose tris(3,5-dimethylphenylcarbamate) CSP in NP mode. The nanostructure of the CS´s cavity and interaction types participating in the interaction mechanism were proposed based on the obtained chromatographic data, infrared spectroscopy and molecular dynamics simulations [90]. Franco and Zhang proposed a screening procedure for the development of analytical methods for resolution of enantiomers in a reasonable time frame performed on a relatively small set of polysaccharide-based columns [91,92].

Several papers describe various approaches for preparation/synthesis of newly derivatized polysaccharide-based CSPs with an improved stability towards the mobile phase components. Bae *et al*. prepared new polysaccharide-immobilized CSP by surface-initiated atom transfer radical polymerization; the enantioselectivity was evaluated by injecting ten racemates under NP conditions [93]. The one-pot method was carried out to synthesize the cellulose 3,5-dichlorophenylcarbamates bearing small amounts of 3-(triethoxysilyl)propyl residues and immobilized onto silica gel through polycondensation. The new CSP was tested with eight racemic mixtures using eluents (chlorophorm, THF) which can not be used with conventional coated CSPs [94]. The one-pot method was also applied to the preparation of the cellulose and amylose 3,5-dimethylphenylcarbamates bearing 4-(trimethoxysilyl)phenyl groups and immobilized onto silica gel through polycondensation of the trimethoxysilyl groups. The enantiorecognition abilities of these columns were examined in the mobile phases containing chlorophorm and THF [95]. Other new CSPs were prepared by immobilization of 3,5-dimethylphenylcarbamates of cellulose and amylose onto silica gel using (3-glycidoxyprolyl)triethoxysilane as a linker. In addition, these CSPs were proven to be compatible with mobile phases containing chlorophorm and THF [96]. Two novel coated composite CSPs were prepared using tris(3,5-dimethylphenylcarbamate) of cellulose and amylose by coating the corresponding derivatives onto 3-aminopropyl silica gel separately and then mixing or by coating the mixed derivatives onto silica gel. The enantioselectivities of these novel CSPs were compared with CSPs containing only one derivative by separation of eight racemates under NP conditions [97]. New cellulose derivatives bearing pyridyl and bipyridyl residues CSPs were also synthesized. These CSPs were used in ligand-exchange chromatography (LEC) for the direct separation of amino acids with mobile phase containing a copper salt [98]. The cellulose derivatives with pyridyl 1 and bipyridyl 2 residues at the 2-, 3- and 6-positions of the glucose ring show low chiral recognition ability while the regioselectively substituted derivatives exhibited relatively high chiral recognition ability. The other new amylose derivatives CSPs bearing different groups were prepared and their enantioselectivities were compared with commercially available polysaccharide columns [99,100]. Novel amylose esters (cinnamate derivatives) CSPs were prepared and evaluated for their application in chiral separations; the recognition of the abilities of these CSPs vary significantly depending on the type and position of substituents on the phenyl group [101].

Chiral screening strategies on diverse columns including polysaccharide-based ones (Chiralcel OD-H, OJ-H, Chiralpak IA-3, IC-3) were described using a set of 19 racemates in isocratic and gradient elution modes with mobile phases compatible using MS detection and suitable for preparative chromatography [102].

2.1.3. Macrocyclic antibiotics-based CSPs

Macrocyclic antibiotics-based CSPs represent another powerful group of CSPs with wide application possibilities. They can be used in RP, NP and PO separation modes. The best separation efficiency and selectivity is achieved mainly with PO mobile phases or in RP separation systems.

Chirobiotic T, T2 (both teicoplanin-based) and TAG (teicoplanin aglycone-based) columns were used to separate the enantiomers of five monoterpene-based 2-amino carboxylic acids under RP conditions [103]. Underivatized γ-amino acids were enantioseparated in RP HPLC systems with a Chirobiotic T, T2, TAG and R (ristocetin A-based) columns, mechanism of chiral recognition were discussed [104]. The complementary of new dalbavancin CSP to the teicoplanin CSP

was examined and verified by enantioseparation of 250 structurally different racemates using three mobile phase compositions [105]. A RP18 monolithic column coated with N-(2-hydroxydodecyl)-vancomycin was prepared and successfully applied to the enantioseparation of dansylamino acids [106]. A two-dimensional HPLC method using a C18 column and teicoplanin CSP under RP conditions was applied for the determination of three pairs of amino acids, *i.e.,* tyrosine, phenylalanine, tryptophane, in order to control transformations in the E-beam irradiated foodstuff [107].

2.1.4. Protein-based CSPs

Protein-based CSPs are used less frequently for the separation of enantiomers in HPLC. Their main disadvantage is their limited compatibility with mobile phases containing higher amounts of organic modifier. However, they can serve as a model environment for studies of drug interactions in organisms (human body).

New simplified, efficient and generic protocols for sample screening on CHIRAL-AGP column (utilizes α_1-acid glycoprotein as CS) for liquid chromatoghraphy with MS detection (LC-MS) analyses in RP mode were developed [108]. Chrysanthakopoulos *et al*. studied the retention behavior of 39 structurally diverse drugs on human serum albumin CSPs (HSA CSP) in RP mode for the calculation/simulation of plasma protein binding data [109]. A Chiralpak AGP column was successfully used for the separation of a mixture of racemic pharmaceuticals using mobile phase composed of 1% propane-2-ol in 10 mM ammonium acetate, pH 5, compatible with MS detection [110].

2.1.5. Pirkle-type CSPs

The π-donor or π-acceptor CSPs belong to the oldest applications in chiral HPLC separations. Nevertheless, it is still used in various combinations. Both commercially available and newly π-donor acceptor modified CSPs appear in the literature.

Adsorption of naproxen enantiomers on (*R,R*) Whelk-O1 and (*S,S*) Whelk-O1 CSPs were studied in RP mode; the mechanism of adsorption and separation is also discussed [111,112]. The enantioseparation of vesamicol and six new azaspirovesamicols was accomplished on two Pirkle-type columns, *i.e.,* Reprosil Chiral-NR (π-donor acceptor) and Reprosil Chiral-OH (π-donor acceptor, esp. for aromatic alcohols) and compared with other types of CSPs – teicoplanin aglycone, cellulose and amylose-based CSPs [113]. The inverted chirality columns approach was used for the determination of enantiomeric excess of camptothecin derivative – namitecan in the systems with (*R,R*) Whelk-O1 and (*S,S*) Whelk-O1 CSPs [114]. (*S,S*) ULMO column (based on a 3,5-dinitrobenzoyl derivative of diphenylethylenediamine) were used for the semipreparative enantioseparation of four axially chiral biscarbostyrils (4,4´-bisquinoline-2-ones). For this specific case three different calculation methods of dynamic peak shape were compared [115]. A new Pirkle-type CSP was prepared using Sepharose 4B as a matrix, L-tyrosine as a spacer arm, and the aromatic amino derivative of L-glutamic acid as ligand and applied to resolution of (±)-β-methylphenylethylamine [116].

Two brush-type CSPs of single selector were synthesized by immobilization of ((2*S*,3*S*)-1-(benzyloxy)-4-chloro-1,4-dioxobutane-2,3-diyl)dibenzoate and (1*R*,2*R*)-1,2-diphenyl-2-(3-phenylureido)ethyl 4-isocyanatophenyl urea CSs on aminated silica gel; a combination of these both CSs was also immobilized on aminated silica gel to prepare a mixed CSP. The columns were tested by enantioseparation of various analytes in RP mode [117]. Three novel brush-type CSPs differing in the size of silica particles (4.3 μm, 2.6 μm, 1.9 μm) were prepared by covalent grafting of the π-acidic bis(3,5-dinitrobenzoyl)-derivative of trans-1,2-diaminocyclohexane. The enantioselectivity of these CSPs were tested using different pairs of enantiomers [118].

2.1.6. Crown ether CSPs

As these CSPs can be used for a limited group of enantiomers they did not gain an important position among chiral stationary phases with a wide application field. In addition, crown ether-based CSPs were not employed in many papers dealing with liquid chromatography during this review period.

CSP based on (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid was applied to the resolution of 1-aryl-1,2,3,4-tetrahydroisoquinolines in PO mode [119]. The same CSP under PO conditions was used to resolve flecainide (antiarrythmic drug) and its analogues [120] and for the separation of native diaminopimelic acid stereoisomers in RP mode [121]. Doubly tethered CSP based on (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid was used for the enantioseparation of tocainide (antiarrythmic drug) and its analogues in RP HPLC, the influence of mobile phase composition and temperature on enantioseparation was examined [122].

2.1.7. Cyclofructan-based CSPs

Cyclofructan-based chiral selectors were introduced in 2009 [123]. The cyclofructan-based chiral stationary phases (CF CSPs) offer a crown ether core for interaction with analytes. While native CF CSPs have just very

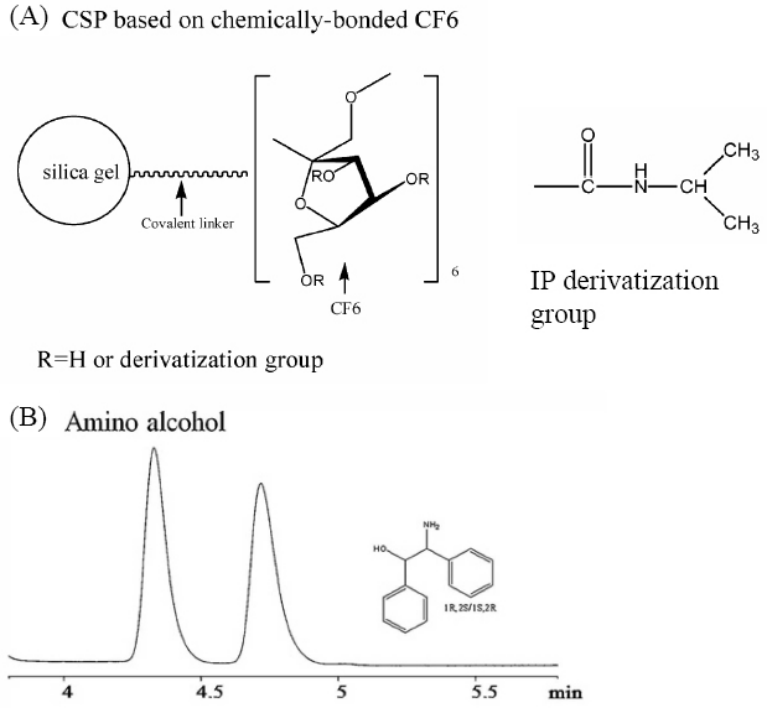

Figure 1. (A) Scheme of chemically bonded derivatized-CF6 CSP and chemical structure of isopropyl (IP) derivatization group. Reprinted with permission from [125], Copyright (2011) American Chemical Society. (B) Chromatogram of enantioseparation of primary alcohol 2-amino-1,2-diphenylethanol. CSP : isopropyl functionalized CF6, mobile phase composed of ACN/MeOH/acetic acid/triethylamine 30/70/0.3/0.2. Reprinted from [129], Copyright (2011), with permission from Elsevier

limited enantioseparation abilities their derivatized analogs were shown to give good resolution for various enantiomers.

The interaction possibilities of *R*-naphthylethyl cyclofructan 6 CSP in NP mode were revealed by linear free energy relationship (LFER) method and compared with those of *R*-naphthylethyl-β-CD CSP; chiral separation of binaphthyl catalysts was examined [124]. *R*-naphthylethyl cyclofructan 6 and dimethylphenyl cyclofructan 7 CSPs were reported to provide enantioselectivity for a broad range of compounds, *e.g.* chiral acids, amines, metal complexes, neutral compounds [125]. Native cyclofructan 6 is suitable for achiral separation of polar compounds in HILIC mode [126]. Isopropyl functionalized cyclofructan 6 CSP (Fig. 1A) demostrate a high efficiency for enantioseparation of compounds possessing primary amino groups (Fig. 1B) [127].

2.1.8 Polymeric CSPs

Polymeric CSPs keep effort to find their position in the enantioselective separation science. In general, results obtained using CSPs based on naturally occurring CSs (or just their modifications) give better results.

New polymeric chiral stationary phases based on the monomers: N-(2-acryloylamino-(1*R*,2*R*)-cyclohexyl) acrylamine (P-CAP CSP), N,N´-[(1*R*,2*R*)-1,2-diphenyl-1,2-ethanediyl]bis-2-propenamide (P-CAP DP CSP) and trans-9,10-dihydro-9,10-ethanoanthracene-(11*S*,12*S*)-11,12-dicarboxylic acid bis-4-vinylphenylamide (DEAVB CSP) were used for the enantioseparation of 17 chiral organic sulfoxides in three separation modes [128], with the best enantioselectivities were obtained under NP conditions**.** Three new polymeric CSPs were synthesized based on (1*S*,2*S*)-1,2-bis(2,4,6-trimethylphenyl)ethylenediamine, (1*S*,2*S*)-1,2-bis(2-chlorophenyl)ethylenediamine, and (1*S*,2*S*)-1,2-di-1-naphthylethylenediamine *via* a simple free radical initiated polymerization in solution. Their enantioselectivities were evaluated by the separation of various racemates (amines, amides, alcohols, amino acids, ester *etc.*) in NP mode and compared with structurally related commercial P-CAP-DP CSP [129]. Two helical polyisocyanide-based CSPs covalently bonded to silica gel (polyisocyanides are composed of the same L-alanine repeating units, but they are completely different in their helical sense (right- and left-handed helices)) were prepared and chiral separation of 15 structurally different compounds were investigated in NP mode [130].

2.1.9. CSPs for ligand/ion exchange chromatography

LEC represents one of the oldest environments used for the separation of enantiomers. The simplest system can be created using one enantiomer of an amino acid (as chiral ligand) and mostly Cu(II) as a central atom forming the complex with another amino acid as analyte.

The click chemistry was applied to immobilize L-prolinamide derivative onto azide-modified silica gel to obtain a novel CSP for ligand exchange chromatography; the CSP was evaluated by enantioseparation of some amino acids [131]. Proton pump inhibitors, *i.e.,* omeprazole, pantoprazole, lansoprazole, rabeprazole were enantioseparated using ligand exchange CSP prepared by bonding (*R*)-phenylglycinol derivative, sodium N-[(*R*)-2-hydroxy-1-phenylethyl]-N-undecylaminoacetate, to silica gel [132].

LEC is often performed using achiral columns and mobile phases with chiral additives. Ofloxacin enantiomers were enantioseparated in the system with a C18 column and a mobile phase composed of methanol/water containing different concentrations of L-isoleucine and copper sulfate [133] or a C18 column and a mobile phase composed of methanol/water containing L-1 amino acid ionic liquid and copper sulfate [134]. Racemic amino acids (valine, methionine, leucine, phenylalanine and tyrosine) were separated on RP-C8 column with aqueous mobile phase containing N,N-dimethyl-L-phenylalanine and copper [135]. The influence of non-ionic surfactants on the selectivity and retention were also examined [136]. A chiral LEC was applied to the separation of four glutamate analogs (1-aminospiro [2.2]pentyl-1,4-dicarboxylic acids) first on a CSP obtained by dynamic coating of C18 with *S*-trityl-(*R*)-cysteine, and then in chiral mobile phase prepared from O-benzyl-(*S*)-serine [137]. Enantiomer elution order of amino acids in chiral LEC was elucidated by computational studies [138].

Novel anion exchange 1,2,3-triazole-linked CSPs were prepared by click chemistry of 10,11-didehydrocinchona *tert*-butylcarbamates to azido-grafted silica gels. These CSPs were tested under PO and RP conditions with a set of structurally diverse racemates (acids, N-protected amino acids, aromatic and aryloxycarboxylic acids, binaphtholphosphate) [139]. Ion chromatography with cation exchange column employing crown ether and carboxylate and phoshonate cation exchange sites was applied for determination of imidazolium and pyridinium ionic liquid cations [140].

2.1.10. Miscellaneous CSPs

Chiral macrocycles with a hydrogen bond donor/acceptor site in the cavity were synthesized and covalently bonded to silica gel to give five different CSPs. These phases showed excellent abilities to separate various chiral compounds, *e.g.* ketones, esters, carboxylic acids, amines *etc.* [141]. Four novel dendrimer-type CSPs were prepared by immobilizing (1*S*,2*R*)-1,2-diphenyl-2-(3-phenylureido)ethyl 4-isocyanatophenylcarbamate on dendrimers of various generations (Fig. 2), and the chiral separation of structurally diverse analytes were performed in RP and NP modes [142]. Two new quinine-based CSPs, *i.e.,* QN CSP and QN CSP (EC) were developed by the immobilization of quinine on porous silica particles, one CSP was subsequently endcapped with n-hexyl hydrocarbon chains. The enantioselectivity was evaluated by the separation of twenty N-derivatized 2,4-dinitrophenyl α-amino acids in RP mode [143]. Enantioseparation of an amino acid derivative phthalylvaline was achieved on quinine-carbamate based CSP, the effect of mobile phase composition was investigated [144].

3. Electromigration methods

Recent reviews pursuing a survey of enantioseparations performed in various electromigration systems are listed in Table 2.

3.1. Recent enantioselective capillary electrophoresis

While the chromatographic part of this review is simply divided into subchapters according to different structure/chemistry of chiral stationary phases, a similar approach is not possible in the electrophoresis chapter. In this part the sort is based on the subject of the paper reviewed, electromigration methods utilized and only then on the chiral selectors used.

3.1.1. Theory and recognition mechanism

Some physico-chemical studies were carried out to determine the CS-analyte interaction constants and to create mathematical models for the explanation of a separation mechanism and/or prediction of separation behavior and chiral recognition.

The method for the determination of a rate constant of interconversion of enantiomers in chiral and achiral environments of a dynamic enantioseparation system was evaluated in terms of its accuracy, sensitivity and robustness [186]. Two different enantioseparation systems were selected and compared statistically. Clarification of enhanced selectivity in CZE multi-chiral selector systems, namely mixtures of highly sulfated β-cyclodextrins (HS-β-CDs), as compared with single-isomer CD was reported by Dubsky *et al.* [187]. The presumptions resulting from the theoretical

Table 2. Review articles dealing with chiral separations in capillary electrophoresis methods published in the period between January 2008 and May 2011.

Methods	Chiral selector*	Topic; Group of analytes	Ref.
CE, HPLC		developments and applications	[5,31]
CE, HPLC, GC		general strategies, suitable for beginners	[145]
CE, NACE, CEC, chip-CE		chiral separation principles, developments, applications, new chiral selectors	[146]
CZE, NACE, MEKC, MEEKC, CEC		chiral and non-chiral analyses of phytochemical substances	[147]
CE, CCE, CEC		separation principles, chiral recognition mechanisms, applications to drugs	[148]
ligand exchange in CE, HPLC, CEC		essential papers, authors´ own activities	[2]
CE-MS		electrolytes systems for chiral separations	[149]
CE-MS		chiral separations of amino acids	[150]
EKC-MS		various approaches of on-line coupling	[151]
CE-MS		enantiomeric analysis of compounds in different matrices	[152]
MEKC		classical and newly used pseudo-stationary phases	[153]
MEEKC		advances in chiral separations	[154-156]
CE		on-line sample preparation, ultratrace chiral determination of biologically active compounds	[157]
nano-CE, nano-LC		nano scale chiral separations	[158]
CZE, MEKC, CEC		chiral separation of amino acids, pesticides, polyphenols, food compounds	[159]
CE		methodological and instrumental improvements for enhancing sensitivity in chiral analysis	[160]
chip CE		enantioseparations by microchip electrophoresis	[161,162]
NACE		list of chiral separation	[163]
MEKC		innovations of instruments and methodology	[164]
CE, MEKC, MEEKC, CEC, chip CE		enantioseparations of pharmaceuticals, biochemicals, agrochemicals, fine chemicals, specific test compounds, new chiral selectors, separation mechanism	[165]
CE		recent strategies to improve resolution	[166]
MEKC		fundamental characteristics	[167]
CE	CDs	boron cluster species	[168]
LC, CE		fluoroquinolones	[9]
CE, GC, HPLC		commercial organophosphorus pesticides	[8]
CE		active pharmaceutical ingredients	[169]
CE, GC, HPLC, SFC		pyrethroids (synthetic pesticides)	[11]
MEKC		amino acids, several types of biomatrices	[170]
CE		amino acids	[171]
CE, LC		D-isomers of amino acids, biological matrices, various modes of detection	[24]
CE, HPLC, GC		chiral pesticides	[22]
CE, LC		triptamine based drugs	[23]
CE		peptide stereoisomers	[172]
CE		drugs, metabolites, biomarkers in biological samples, new approaches and enantioselective agents, on-line sample pretreatment, detection modes	[173]
CE		environmental pollutants	[174]
CE, LC		andrenergic drugs	[37]
CE, LC		thalidomide and its metabolites	[36]
CE	antibiotics	pharmaceuticals	[175]
CE	crown ethers crown ethers + CDs	chiral and non-chiral applications	[176]
CE	single isomer derivatives of CDs		[177]
CE	antibiotics polysaccharides		[178]
	uncharged CDs	fundamental contributions	[179]

Continued **Table 2.** Review articles dealing with chiral separations in capillary electrophoresis methods published in the period between January 2008 and May 2011.

Methods	Chiral selector*	Topic; Group of analytes	Ref.
	charged CS	major developments	[180]
EKC	polymeric pseudo-stationary phases	chiral and achiral applications	[181]
CE, LC	Penicillin G acylase	stereoselective molecular recognition mechanism	[27]
CE, LC	monosubstituted positively charged CDs	work carried out in authors´ laboratory, amino acids, anionic pharmaceuticals, neutral analytes	[182]
CE	CDs	new derivatives and applications, drug, environmental and food analysis, bioanalysis	[183]
CE, CEC	CDs	recent employment of CDs	[184]
CE	CDs	applicability of CD selectors	[185]

** If the CSs are not stated the review gives an overview of various types.*

multi-CS model were verified experimentally with the enantioseparation of lorazepam in the presence of a commercial mixture of HS-β-CDs and single-isomer HS-β-CD, heptakis(6-O-sulfo)-β-CD. Binding constants of modafinil enantiomers with the sulfated β-CD were determined using the CE technique and three different linear plotting methods[188]. Computational calculations of the complexation energies of inclusion complexes of sulfated β-CD with ofloxacine and ornidazole enantiomers were utilized to elucidate differences between migration times of the both analytes and their enantiomers. The migration order of the enantiomers are reflected in the different complexation energies [189]. Computational modeling based on the calculations of complexation energies of inclusion complexes were carried out to elucidate the migration behavior of the enantiomers of primaquine and quinocide in the presence of α- and β-CD and 18-crown-6-ether as chiral selectors [190]. The epimerization rate constants of amygdalin under basic microemulsion conditions at different epimerization times were determined by the microemulsion electrokinetic chromatography (MEEKC) method [191].

Propranolol was repeatedly used as the test compound for studying the structures of intermolecular selector-analyte complexes. Possible molecular mechanisms of enantioseparation of propranolol in the presence of heptakis(2,3-di-O-methyl-6-O-sulfo)-β-CD (HDMS-β-CD) and heptakis(2,3-di-O-acetyl-6-O-sulfo)-β-CD (HDAS-β-CD) in aqueous and non-aqueous background electrolytes (BGEs) were investigated by CE and rotational frame nuclear Overhauser effect spectroscopy (ROESY) experiments[192]. Major structural differences were found between the propranolol complexes with native β-CD and heptakis(6-O-sulfo)-β-CD by 1D ROESY NMR experiments [193]. The 2D ROESY technique was used for the elucidation of the structures of inclusion complexes of pregabaline derivatives and β-CD [194] and vinca alkaloids with various CDs [195]. High resolution MS and various NMR techniques were utilized to investigate the mechanism of enantioselective recognition of HDAS-β-CD towards propranolol. The enantiomeric nuclear Overhauser effect was observed for the first time. The switch between external complex and inclusion of the propranolol/HDAS-β-CD pair was observed when an aqueous buffer was changed to a non-aqueous methanolic electrolyte [196]. The binding free energies of HP-β-CD with propranolol and its five analogues were calculated by molecular docking. The calculated results were in agreement with experimentally obtained order of *R*/*S* enantiomers [197].

3.1.2. Detection

Detection is an inseparable part of any separation technique. Sensitive detection offering low limits of detection (LOD) and quantification (LOQ) is essential for analytical applications. Therefore, we present the works, in which detection is the main topic in this special chapter.

New on-line coupling of chiral MEKC to atmospheric pressure photoionisation MS (APPI-MS) was reported for the first time. Four structurally similar neutral test solutes (benzoin derivatives) were successfully ionized by APPI-MS [198]. Ligand-exchange capillary electrophoresis (LECE) utilizing 6-mono-deoxy-6-[4-(2-aminoethyl) imidazoyl]-β-CD complexing with copper(II) as chiral selector was hyphenated to electrospray ionisation mass spectrometry (ESI-MS). LECE-ESI-MS gave better values of LOD of tryptophane enantiomers than LECE with ultraviolet (UV) detection [199]. CE-ESI-MS/MS arrangement was used for the determination of D-carnitine as enantiomeric impurity in L-carnitine in pharmaceutical formulations [200] and dietary food supplements [201]. Chiral CE-ESI MS/MS mode was utilized in the enantioseparations of 1,2,3,4-tetrahydroisoquinoline derivatives. To avoid any potential contamination of MS ionisation source with non-volatile chiral selector (sulfated β-CD), a partial filling technique

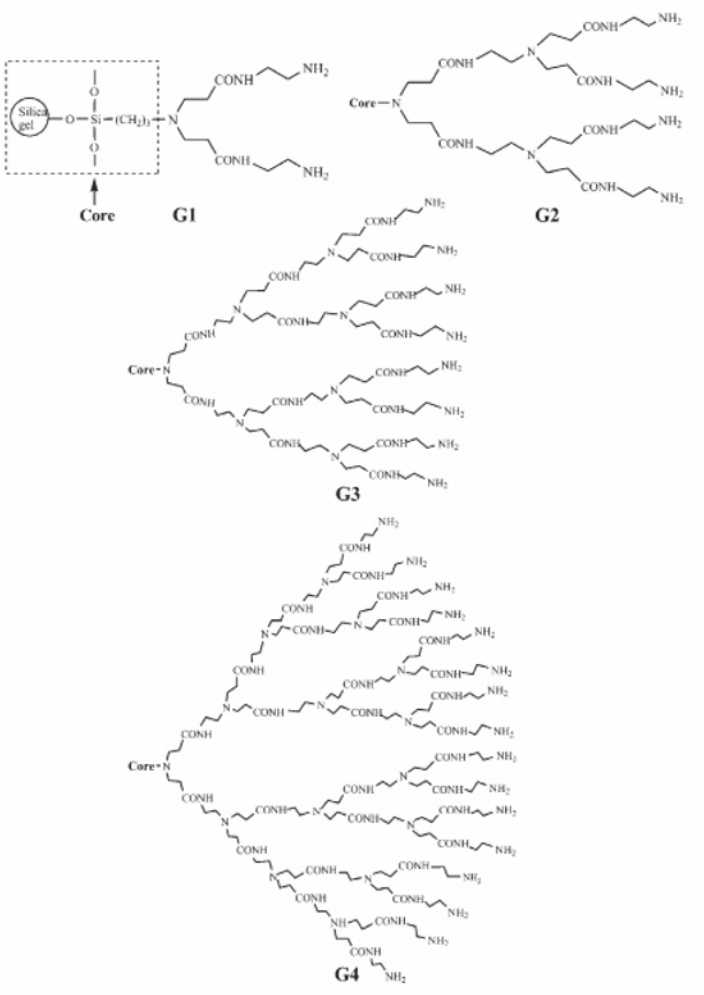

Figure 2. The structure of generation-various dendrimers. G1, G2, G3 and G4 represent one to four-generation dendrimer respectively. Reprinted from [144]. Copyright (2011), with permission from Wiley

was employed [202]. The impact of the BGE composition on the ionization performance in analysis of carvedilol by non-aqueous capillary electrophoresis (NACE) with ESI-MS was investigated under three achiral (ammonium formate, acetate or camphorsulfonate in methanol) and three chiral (addition of HDMS-β-CD, HDAS-β-CD or heptakis(2-O-methyl-3-O-acetyl-6-O-sulfo)-β-CD (HMAS-β-CD)) conditions. The results showed that the chiral selector must be selected not only according to its ability to enantioseparate the compound of interest, but also according to its effect on the ionization efficiency [203]. CE with an end-column amperometric detection was developed for sotalol enantiomers analysis [204]. CE combined with electrochemiluminescence detection was successfully used for enantioseparation of antidepressant trimipramine in aqueous-organic media [205]. A new detection method was introduced for the analysis of the chiral drug, bupropion. The detection was based on the phosphorescence in both the direct mode and the indirect mode. In the indirect mode an analyte acts as an energy donor to the phosphorescent acceptor providing phosphorescence with higher intensity. In this case, biacetyl was utilized as the energy acceptor. LODs of both enantiomers obtained by indirect detection were 40 times lower than those obtained in the direct mode [206]. The detection of non-UV-absorbing α-hydroxy- and amino-substituted alkylcarboxylate enantiomers were achieved by capacitively coupled contactless conductivity detection (C^4D). Derivatization of the analyzed compounds was not necessary when C^4D was used [207]. Two C^4D detectors were utilized in heart-cutting 2D-CE method for chiral separation of native amino acids [208]. Light-emitting diode-induced fluorescence detection (LEDIF) was used for recording D- and L-Asp enantiomers. D- and L-Asp were derivatized with naphthalene-2,3-dicarboxaldehyde to form fluorescent derivatives prior to CE-LEDIF [209].

3.1.3. Sensitivity enhancement by preconcentration

Sensitivity of an analytical method (detection) can be also improved either by derivatization or using a preconcentration step.

Wang *et al*. [210] developed CE method combining a partial filling technique with large volume sample stacking. The method was applied to the enantioseparation of racemic fenoprofen and six 9-fluorenylmethyl chloroformate amino acid derivatives. Under the optimized electrokinetic injection and separation conditions, an almost 1000-fold enhancement in detection sensitivity compared to the normal injection was achieved. Two on-line preconcentration methods: (i) hyphenated MEKC stacking with reverse migrating micelles (SRMM), and (ii) sweeping were used to improve LOD of three triazole fungicides [211]. Poly(ethylene oxide) (PEO) zone was utilized as a concentrating medium during enantiomeric separation of D- and L-aspartic acid by cyclodextin-modified MEKC (CD-MEKC). Migrating sodium dodecylsulfate-analyte (SDS-analyte) complexes were slowed down in the PEO zone and stacked through the viscosity difference between PEO and the sample zone. Approximately 100-fold improvement in the sensitivity of D- and L-aspartic acid detection was achieved [209]. On-line sample preconcentration step, field-amplified sample injection (FASI), substantially improved values of LODs of D,L-tetrahydropalmatine enantiomers and enabled analysis of a real sample [212]. Transient moving chemical reaction boundary (tMCRB) was investigated as the on-line preconcentration possibility for native amino acids in heart-cutting 2D-CE. The first dimension of the heart-cutting 2D-CE provided a non chiral separation and isolation of the fraction of interest and the second dimension rendered chiral separation of the selected amino acid. The LODs were improved by a factor of 10 using the tMCRB focusing step [208].

3.1.4. C(Z)E

In the literature the capillary electrophoresis system with a CS in a BGE is considered either as a CZE with chiral additives or as electrokinetic chromatography (EKC) with chiral pseudostationary phase. We decided to keep the classification used by the authors themselves in their papers and put these works together in one chapter entitled C(Z)E.

3.1.4.1. Cyclodextrins

CD derivatives belong to the most popular group of chiral selectors used in CE. Enantioseparations using the well-established and/or newly designed and prepared derivatives regularly appear in the literature. CDs can be applied in all possible separation modes – CZE, MEKC, MEEKC, CEC.

Several CD derivatives were evaluated for their ability to separate a series of fifteen racemic 4,5-disubstituted imidazole compounds by CE. The mechanism of the chiral recognition was discussed [58]. Hydroxypropyl-γ-CD (HP-γ-CD) was revealed as the most effective chiral selector towards iodiconazole, a new antifungal drug, and its analogues [213]. Sulfobutyl ether-β-CD was utilized for the determination of enantiomeric purity of a new antiarrhytmic agent marked RS86017. The optimized method was validated [214]. Zhu *et al*. separated sibutramine enantiomers by either methyl-β-CD or carboxymethyl-β-CD (CM-β-CD) as chiral selectors [215]. This research group also investigated the reversal of the enantiomer migration order in CE based on separations of sibutramine as a function of the concentration of native β-CD and acetyl-β-CD [216]. 1,2,3,4-tetrahydroisoquinoline derivatives, neurotoxins inducing Parkinsonism, were baseline enantioseparated by CE-ESI-MS/MS with sulfated β-CD as CS. The resolution values were better than those reported previously by a HPLC method [202]. In order to evaluate the enantioselective binding of zoplicone enantiomers to human serum albumin (HSA), the EKC with partial filling of the anionic CM-β-CD as chiral selector was applied. The results suggested that *S*-zopiclone exhibits twice the affinity to HSA than *R*-zopiclone [217]. The selection of 22 neutral and anionic CDs were screened in terms of their ability to effectively separate the enantiomers of five antimalarial drugs [218]. Neutral and anionic CDs were also tested for the enantiomeric separation of benzoxazolinone amino alcohols and their aminoketone precursors [219]. A method for the simultaneous analysis of *R*-(−)-, *S*-(+)-baclofen and an impurity (4*R,S*)-4-(4-chlorophenyl)pyrrolidin-2-one utilizing α-CD as CS was established. A PEO-coated capillary was used and an optimized method was validated [220]. The comparison of β-CD, γ-CD, dimethyl-β-CD (DM-β-CD), heptakis(2,3,6-tri-O-methyl)-β-CD (TM-β-CD) and HP-β-CD for their ability to separate fenoterol enantiomers were reported and the obtained results were compared with HPLC experiments [86]. A novel single isomer of positively charge β-cyclodextrin, mono-6-deoxy-6-((2*S*, 3*S*)-(+)-2,3-O-isopropylidene-1,4-tetramethylenediamine)-β-CD was designed and synthesized. The chiral resolution capabilities of a new chiral selector were studied using 10 dansylamino acids as model analytes [221]. Native α-, β-, and γ-CDs and their hydroxypropylated, randomly methylated, carboxymethylated and sulfobutylated derivatives were used for the enantioseparations of three vinca alkaloid enantiomers (vincamine, vinpocetine and vincadiformine). All vinca alkaloids were successfully enantioresolved but with different CDs [195]. HP-β-CD among other tested CDs (γ-CD, β-CD, DM-β-CD)

provided the best resolution of pheniramine enantiomers [222]. The method was subsequently modified using a partial filling approach that resulted in improved resolution [223]. CE method with sulfated β-CD as chiral selector for the separation of enantiomers of ofloxacin and ornidazole was described. The optimized method was validated and applied for the determination of these analytes in a pharmaceutical formulation [189]. Several CD derivatives (single carboxymethyl-α-, β- and γ-CDs or sulfobutyl-β-CD) were examined to find the most selective system for enantioseparations of 19 pairs of cis-β-lactam stereoisomers of pharmacological importance. From the tested chiral selectors the sulfobutyl-β-CD yielded the best results [224]. A new single-isomer cationic β-cyclodextrins, namely mono-6-deoxy-6-pyrrolidine-β-CD chloride (pyCDCl), mono-6-deoxy-6-(N-methyl-pyrrolidine)-β-CD chloride (N-CH_3-pyCDCl), mono-6-deoxy-6-(N-(2-hydroxyethyl)-pyrrolidine)-β-CD chloride (N-EtOH-pyCDCl), mono-6-deoxy-6-(2-hydroxymethyl-pyrrolidine)-β-CD chloride (2-MeOH-pyCDCl) were synthesized (see Fig. 3A) and used as chiral selectors for the enantioseparation of carboxylic and hydroxycarboxylic acids and dansyl-amino acids. The pyCDCl CS exhibited the greatest resolving ability (Fig. 3B) [225]. CE was utilized for the enantioseparation of seven Tic-hydantoin sigma-1 agonists as an alternative technique to HPLC. The enantiomers were fully resolved with HS-β-CD [226]. The enantiomers of pregabalin derivatized by tosyl- and dansyl-chloride were separated using CD modified CE. The best resolution was obtained using 6-monodeoxy-6-mono-(3-hydroxy)-propylamino-β-cyclodextrin hydrochloride for the tysolated derivate and trimethylated α- and β-CDs for dansylated prebalin [194].

3.1.4.2. Oligosaccharides, polysaccharides

Glycogen, a branched polysaccharide, was introduced as a novel chiral selector. The enantioseparation potential of glycogen (an electrically neutral compound) was tested with one acidic and four basic drugs. The enantiomers of citalopram, cetirizine, nefopam and ibuprofen were baseline separated and partial separation of enantiomers of amlodipine was achieved [227]. Chondroitin sulfate A (CSA), a linear ionic polysaccharide, was used as a chiral selector in the enantioseparation of nefopam hydrochloride by affinity electrokinetic chromatography (AEKC). The selector concentration, pH of the BGE, capillary temperature and applied voltage were systematically optimized in order to obtain the optimum separation of the nefopam enantiomers. A statistical analysis approach revealed that the buffer's pH was the most significant parameter controlling the chiral separation. The enantiorecognition mechanism of CSA towards the enantiomers of nefopam was described [228]. Carboxymethylated cyclosophoraose (CM-Cys) was synthesized and employed as a chiral selector in the enantioseparation of flavonoids [229]. α-Cyclosophorooctadecaose (α-C18), produced by *Rhodobacter sphaeroides*, was successfully isolated and used as chiral selector in the enantioseparation of catechin [230] and five flavanones and three flavanone-7-O-glycosides [231]. Maltodextrin was employed as a chiral selector in the separation of the enantiomers of cetirizine and hydroxyzine in spiked human plasma. The effect of zwitterionic property of cetirizine was also investigated and its cationic form was proven to be advantageous for enantioseparation [232].

3.1.4.3. Antibiotics

Antibiotics represent a very popular group of CSs with a high chiral discrimination power. Their disadvantage is they absorp at the wavelengths usually used for detection of analytes.

Two new chiral selectors from the antibiotic family of macrolides were used within the period of interest for the first time. Erythromycin lactobionate, the structure is depicted in Fig. 4, showed an excellent ability to enantioseparate of the enantiomers of N,N-dimethyl-3-(2-methoxyphenoxy)-3-propylamine, propranolol and duloxetine, while just a partial enantioresolution of primaquine, chloroquine and nefopam [233]. Azithromycin, a semi-synthetic macrolide antibiotic derived from erythromycin, was employed for the enantioseparation of five chiral drugs and tryptophane [234]. Chiral separations of racemic fenoprofen and six 9-fluorenylmethylated acetic acids were achieved employing vancomycin as chiral selector [210]. The same CS was used for the enantioseparations of α-hydroxy- and amino-substituted alkyl carboxylate enantiomers [207]. Three vancomycin-type macrocyclic antibiotics, *i.e.,* balhimycin, bromobalhimycin and dechlorobalhimycin, were used for enantioseparation of N-benzolyated amino acids. Enantioseparation of N-benzoylated derivatives of four amino acids (Leu, Ala, Met and Thr) were compared using a CE method, which combined partial filling approach with a dynamic coating technique and the co-electroosmotic flow (co-EOF) electrophoresis method. The enantiorecognition mechanism was investigated [235].

3.1.4.4. Miscellaneous

Bovine serum albumin was added to a buffer solution to achieve the enantioseparation of D,L-tetrahydropalmatine. Partial filling technique was used to decrease the UV absorption of BGE [212]. Chiral

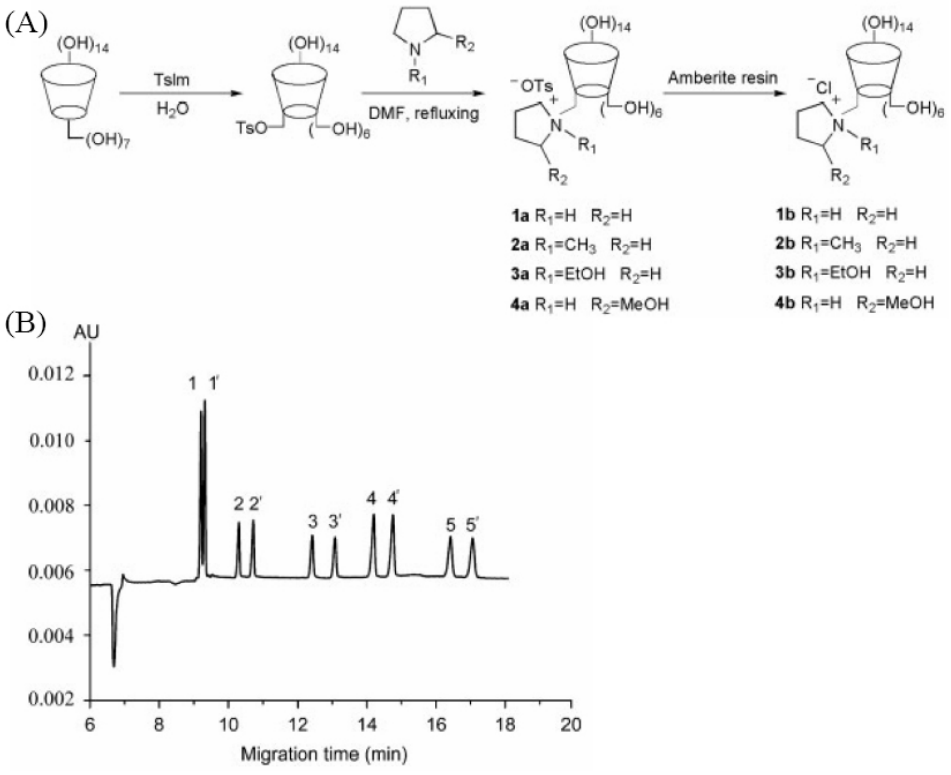

Figure 3. (A) Synthesis of alkyl pyrrolidine substituated single isomer CDs. (B) Enantioseparation of a mixture of five pairs of analytes. 50 mM phosphate buffer, pH 7.0, with 5 mM pyCDCl as chiral selector. (1) dansyl-D,L-serine; (2) 2-(4-hydroxyphenoxy)propionic acid; (3) 2-phenoxypropionic acid; (4) p-hydroxymandelic acid; (5) mandelic acid Reprinted from [225]. Copyright (2011), with permission from Wiley

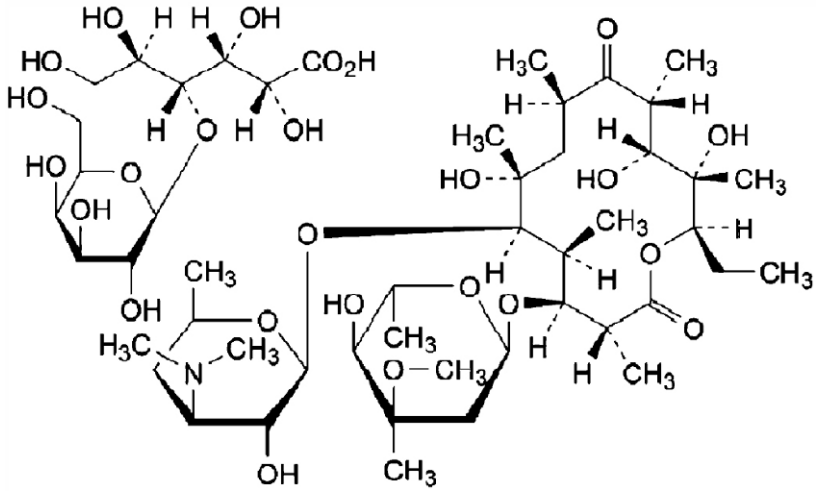

Figure 4. Structure of erythromycin lactobionate, a new antibiotic chiral selector. Reprinted from [233] with kind permission from Springer Science + Business Media.

selector (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid was employed in the second dimension of heart-cutting 2D-CE to enantioseparate D,L-phenylalanine and D,L-threonine in a mixture of 22 native amino acids [208]. The possibility of using N-blocked bivalent dipeptides, known as chiral mobile phase additives in HPLC, as ion-pairing agents in CE for both non-chiral and chiral separation of amino alcohols was shown [236].

Ionic liquids can be used as BGE additives. However, their exceptional properties become obvious only if they are used solely. The ephedrine-based chiral ionic liquid, (+)-N,N-dimethylephedrinium-

bis(trifluoromethanesulfon)imidate ($[DMP]^+$ $[Tf_2N]^-$), was introduced as chiral selector into non-aqueous separation solution consisting of acetonitrile and methanol. Rabeprazole and omeprazole were enantiosepareted and the effects of the $[DMP]^+$ $[Tf_2N]^-$ concentration, the buffers and the choise of organic solvents were studied. The discussion of separation mechanism was further undertaken [237]. The new fluorescent chiral ionic liquid, L-phenylalanine ethyl ester bis(trifluoromethane) sulfonimide, capable of acting simultaneously as solvent, chiral selector and fluorescent agent in chiral analytical measurements was introduced and properties of the separation system were studied [238].

3.1.4.5. Dual selector systems

If optimization of an enantioseparation system with one chiral selector fails, a dual selector system can be employed. However, in many cases well optimized separation with one CS can yield the same or even better results. Many chiral reagents including cyclodextrins and their derivatives, crown ethers, proteins, chiral surfactants and chiral polymers were used in dual selector systems for the enantioseparation of a series of chiral compounds.

The first investigation of an enantioselectivity of dual selector system, which contained a polysaccharide glycogen, was published. Three dual systems combined glycogen with CSA, β-CD and HP-β-CD were tested. The dual system of glycogen with CSA exhibited good enantiodiscriminative properties towards the tested drugs (duloxetine, cetirizine, citalopram, sulconazole, laudanosine, amlodipine, propranolol, atenolol, nefopam). Enhanced enantioselectivity compared to the single selector systems was observed [239]. A CE assay for the simultaneous determination of charged and uncharged potential impurities (1*S*,2*S*-(+)-norpseudoephedrine, 1*R*,2*S*-(–)-norephedrine, phenylacetone and phenylacetone oxime) of dexamphetamine sulfate including the stereoisomer levoamphetamine was developed and validated. Dual CD system consisting of sulfobutyl ether-β-CD and sulfated β-CD was employed [240]. The simultaneous separation of the stereoisomers of six tetrahydronaphthalenic derivatives (agonists and antagonists for the melatonin binding sites) were successfully achieved using a dual CD system in a capillary dynamically coated with PEO. The HS-β-CD/γ-CD system was proven to be the optimal system for this analysis [241]. Enantioselective abilities of various dual CD selectors (carboxymethyl- and sulfobutyl-β-CDs with neutral β-CDs) towards 19 pairs of cis-β-lactam derivatives were tested. Mixtures of TM-β-CD and the negatively charged sulfobutyl-β-CD were able to separate all the investigated stereoisomeric pairs [224]. HDMS-β-CD with β-CD was used as a dual CS system for the separation of methamphetamine and its related compounds. The main aim of this work was to compare the reproducibility of the analysis obtained in three different capillaries – untreated capillary, poly(vinyl alcohol) (PVA)-coated capillary and a capillary with diol groups. The relative standard deviations of the migration times of analytes were lower for diol- and PVA-coated capillaries (0.1%) than for the untreated one (0.4%) [242]. Single isomer CD and dual CDs systems (phosphated-β-CD with HP-γ-CD) were tested for enantioseparation of tysolated and dansylated pregabalins. The resolution obtained with two enantiomers became better only in a dansyl-pregabalin in acidic environment [194]. An Zn(II)-L-valine complex as chiral selector with the addition of β-CD is another example of a dual CS systems [243]. The presence of CD enhanced enantioselectivity of the LECE system.

3.1.5. LECE

Special separation systems utilizing formation of complexes, in which mostly Zn(II) or Cu(II) serve as central ions and pure enantiomer CS and analyte as ligands, were introduced as early as in 1971 [244] and are still utilized today.The novel chiral selector, Zn(II)-L-prolinamide, was used in a kinetic study of the competitive effect of sodium benzoate on D-amino acid oxidase activity [245]. Aldo-bis-indole derivatives (aldo-BINs) of common monosaccharides were prepared and separated by CE. The enantioseparation of the D,L-pairs of aldo-BINs based on ligand-exchange mechanism was achieved using HP-β-CD as a chiral ligand and borate buffer, where borate anion served as central ion. The usefulness of UV active aldo-BINs for sugar composition analysis was demonstrated [246]. Similarly, the D,L-aldo-naphthylimidazoles (aldo-NAIMs) of various D,L-monosaccharide pairs were prepared and enatioresolved utilizing borate buffer and phosphate buffer with sulfated-α-CD [247]. The separation performance of a new ligand-exchange selector di-L-valinol-copper complex was tested on enantioseparations of D,L-dansyl-amino acids, unmodified amino acids racemates and a β-blocker *R,S*-propranolol by LECE in thermoreversible low molecular weight organogel (LMOG) – trans-(1*S*,2*S*)-1,2-bis-(dodecylamido) cyclohexane. The enantioseparation achieved was proven to be superior to MEKC under similar operating conditions [248]. To separate D,L-isocitric acid enantiomers, D-quinic acid was used as a chiral selector ligand and Mn(II), Fe(III),Co(II), Ni(II), Cu(II), and Zn(II) ions were utilized as the central ions. D,L-isocitric acid was found to be enantioseparable with all the above mentioned metal ions except for Mn(II)

[249]. Different cyclodextrins were employed in chiral LECE because CDs can form inclusion complexes and thus enhance the regiospecificity and stereospecificity. The successful separations of 20 pairs of D,L-amino acids with Zn(II)-L-valine complex in the presence of β-CD were achieved. Furthermore, the kinetics of L-amino acid oxidase enzyme reaction was measured in the proposed dual CS system [243]. Dependence of enantioseparation of tartaric acid on molar ratio of Cu(II)/D-quinic acid was studied. At low (1/1 – 1/3) and high (1/8 – 1/12) molar ratios tartaric acid was enantioresolved, but at medium molar ratios chiral separation was not achieved. Reversed enantiomer migration order at high molar ratios were explained by changes in the coordination structure of Cu(II) ion with D-quinic acid [250]. Sodium arsenyl-(L)-(+) tartrate, a member of tartrate-based transition metal complexes, was introduced as a CS that showed enantioselective associations with many cationic analytes, including primary, secondary, and tertiary amines. Twenty six amine-containing compounds showed enantioselectivity within reasonable analysis time and 13 of them were baseline separated [251].

3.1.6. MEKC

Micellar electrokinetic chromatography (or micellar capillary electrophoresis (MCE)) is a popular technique suitable for separation of uncharged analytes. The enantioselective environment can be formed with chiral micelles, achiral micelles with chiral additives to BGE or using mixed micelles (micelle complexes composed of achiral micelles and CSs).

The CD-MEKC method with a HP-γ-CD chiral selector and SDS micelles was reported for the enantiomeric separation of econazole [252] and three triazol fungicides (hexaconazole, penconazole and myclobutanil) [211]. The same chiral selector and sodium deoxycholate as surfactant were used for enantioseparation of derivatized dipeptides (Tyr-Phe, Tyr-Leu, Ala-Gln). The dipeptides were precolumn derivatized with naphthalene-2,3-dicarboxyaldehyde [253]. A HP-β-CD mediated MEKC was utilized for the separation of Asp enantiomers. The influence of the molar ratio of SDS to HP-β-CD as well as the total concentration of SDS and HP-β-CD on the enantioresolution was investigated [209]. TM-β-CD in the presence of sodium cholate surfactant enabled enantioseparation of the synthetic pyrethroid cis-bifenthrin by CD-MEKC [254]. Enantioseparation of this pyrethroid was reported for the first time. This method can be used for the determination of cis-bifenthrin in commercial insecticides. Chen and Du [255] modified MEKC method by addition of a novel antibiotic CS – clindamycin phosphate. Different types of anionic surfactants, organic additives and BGE compositions were tested. Excellent separation of the enantiomers of nefopam, citalopram, tryptophane, chlorphenamine, propranolol and metoprolol, and partial enantioresolution of tryptophane methyl ester and cetirizine were achieved with SDS in phosphate buffer and propane-2-ol as an organic modifier. Four chiral photoinitiators, hydrobenzoin, benzoin, benzoin methyl ether and benzoin ethyl ether were simultaneously enantioseparated using a mixture of two chiral molecular micelles polysodium N-undecenoxy carbonyl-L-leucinate (poly-L-SUCL) and polysodium N-undecenoyl-L,L-leucylvalinate (poly-L,L-SULV) [198]. The mixed mode separation method combining MEKC with polyelectrolyte multilayer (PEM) coating procedure was used for both chiral and achiral separations. Sodium poly(N-undecanoyl-L-leucylvalinate) (poly-L-SULV) served as both a chiral molecular micelles creator and an adsorbed chiral polymer layer [256]. Two CD-MEKC methods were developed for simultaneous enantiomeric separation of four chiral polycyclic musks (Galaxolide, Tonalide, Traseolide, and Phantolide). The best separation was achieved with SDS micelles in a dual CD system composed of HP-γ-CD and γ-CD [257].

3.1.7. MEEKC

Three different arrangements for enantioselective separation can be used in microemulsion electrokinetic chromatography. A chiral selector can be deposited on the capillary wall, chiral microemulsion can be used or CS can be added to the BGE.

MEEKC carried out in a capillary coated by β-CD enfolded polymer layer provided higher separation efficiency of stereoisomers of sertraline than MEEKC without the presence of a CD polymer coating [258]. The development and validation of a MEEKC method for enantioseparation of phenethylamines was reported. The separation system consisted of sulfated β-CD added to the microemulsion composed of the oil-component ethyl acetate, surfactant sodium dodecylsulfate, cosurfactant 1-butanol, propane-2-ol as the organic modifier and phosphate buffer as the aqueous phase. The results were compared with those obtained by CD-modified CZE [259]. The preparation of chiral microemulsions from eight L- and D-tartrates with different alcohol moieties as chiral oils was described by Hu *et al*. [260]. A water insoluble compound, di-*i*-butyl L-tartrate, was used for the preparation of a stable microemulsion, which was utilized for the enantioseparations of β-blockers. Yu *et al*. utilized MEEKC for the separation and determination of amygdalin and its epimer (neoamygdalin) [191].

Gold nanoparticles modified by thiolated β-CD were revealed as a suitable pseudostationary phase for the

enantioseparation of four dinitrophenyl-labeled amino acid enantiomers (Val, Leu, Glu and Asp) and three pairs of drug enantiomers (chlorpheniramine, zopiclone, carvedilol) [261].

3.1.8. Microchip capillary electrophoresis

Substantially reduced material needs, therefore low cost of analyses, and small sample amounts required for analysis are the main advantage of miniaturized separation techniques.

The MEKC mode of microchip electrophoresis utilizing SDS micelles in borate buffer for quantitative analyses of fluorescein-5-isothiocyanate (FITC) labeled ephedrine and pseudoephedrine in tablet formulations and urine after oral intake of the drugs was reported. The linearity, reproducibility, and applicability of the method were evaluated [262]. Both achiral and chiral separations of proteins and racemic amino acids were studied on a poly(methyl methacrylate) (PMMA) microchip. Immobilization of amino-poly(ethyleneglycol) (PEG–NH_2) onto surface of the microchip reduced irreversible adsorption of proteins on the wall. Chiral separation of tryptophane was achieved after addition of bovine serum albumin to the background solution [263].

A new method was described for 2D separations using a microfluidic chip normally employed for 1D electrophoresis. Gradient elution moving boundary electrophoresis and chiral CZE were combined as the first and the second dimension of the separation process of some amino acids, respectively [264].

3.1.9. NACE

Non-aqueous capillary electrophoresis represents the possibility for changing the interaction mechanism to extend the range of applicability of a given chiral selector because different interaction types prevail in chiral recognition in aqueous *vs*. non-aqueous environments.

Enantioselectivity of single-isomer anionic cyclodextrin HMAS-β-CD towards basic model analytes were tested under various concentrations of HMAS-β-CD and BGE composition in order to propose a generic system for basic drug analysis [265]. Two single-isomer anionic CDs, HMAS-β-CD and HDMS-β-CD, were utilized simultaneously in chiral and achiral separations of fenbendazole and its sulfoxide and sulfone metabolites [266]. Novel NACE method for the enantioseparation of some β-blockers and β-agonists was developed. Di-n-amyl L-tartrate–boric acid complex, *in situ* synthesized by the reaction of di-n-amyl L-tartrate with boric acid in a non-aqueous BGE using methanol as the medium, was tested as the chiral selector. The enantioseparations of all the tested drugs were achieved [267]. Two new antibiotic CSs were tested in NACE mode. Erythromycine lactobionate with mixed buffer solution containing borate buffer and methanol (50/50, *v/v*) was utilized for enantioseparation of N,N-dimethyl-3-(2-methoxyphenoxy)-3-propylamine, propranolol, duloxetine, primaquine, chloroquine and nefopam [233]. Polar organic mixture composed of acetonitrile, methanol, acetic acid and triethylamine (80/20/0.1/0.1, *v/v/v/v*) was employed as BGE for enantioseparation of five chiral drugs and tryptophane with azithromycin as CS [234]. Non-aqueous mode of capillary electrophoresis was also used for enantioseparation of rabeprazole and omeprazole in presence of ephedrine-based ionic liquid $[DMP]^+[Tf_2N]$ [237].

4. Conclusions

The importance of enantioselective separation methods is reflected in the number of publications in the literature. Both liquid chromatography and electromigration techniques have an irreplaceable position in this field. The crucial factor for the creation of a successful enantioselective separation system is the proper choice of a chiral selector or chiral stationary phase. The choice must be based on the structure of the compounds to be analyzed. The separation system must be considered as a whole because the enantiodiscrimination mechanisms can participate in different separation environments with the same CS/CSP. This review is intended to serve as an aid to support the choice of a chiral selector or a chiral stationary phase.

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