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Chiral Separations: A Review of Current Topics and Trends

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This Review article covers current topics, trends, and applications in chiral separations from January 2010 to September 2011 and is restricted to the English language literature. The separation of enantiomers of chiral compounds continues to be of great interest due to their prevalence in the pharmaceutical industry, agrochemicals, and food additives to name a few. It is well established that enantiomers often exhibit different biological and pharmacological responses. Enantiomers remain a challenge to separate due to their identical physical and chemical properties in an achiral environment, and research on specialized separation techniques continues to be developed to resolve individual enantiomers. As evidenced by the number of articles published in the review period, chiral separations are a mature and widely used technique. While there have been a number of new and novel technologies introduced in the literature during this time period, the number of applications using current or slightly modified techniques also continues to grow.

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

Chiral separations performed by HPLC remain the workhorse of all enantioseparations, with more than half of all articles on chiral separations published in this area. The use of polysaccharide and cyclodextrin chiral stationary phases (CSPs) continues to dominate the majority of all HPLC separations using CSPs. Protein, ligand, and ion exchange, and macrocyclic antibiotic CSPs were also widely used, accounting for approximately a third of all HPLC chiral separations.

Polysaccharide CSPs. The number of publications involving polysaccharide CSPs remained steady from the 2010 Review to this review period, accounting for approximately a third of all HPLC based chiral separations. Most chiral applications are carried out on commercially available columns, with the most commonly used phase on cellulose or amylose being the 3,5-dimethylphenyl carbamate. The Chiralcel OD,[1−4] Lux Cellulose,[5,6] Kromasil CelluCoat,[7] and AmyCoat[8,9] all are 3,5-dimethylphenyl carbamate phases. Another popular phase was the tris cellulose 4-methyl benzoate CSPs, which include Chiralcel OJ and Sino-chiral OJ.[10−12] Other polysaccharide CSPs are cellulose tris 3,5-dichlorophenyl carbamate such as Chiralpak IC[13,14] and amylose (*S*)-α-methylbenzyl carbamate such as Chiralpak AS-RH.[15]

Examples of uses of polysaccharide CSPs include the direct enantioseparation of aminonaphthol analogs possessing two chiral centers on the CelluCoat and AmyCoat CSPs,[8] the chiral resolution of 19 β-lactams on the CelluCoat and AmyCoat CSPs,[9] the separation of enantiomers of paclobutrazol on Sino-chiral OJ CSP,[10] and the role of trace water in aged mobile phases on the enantioseparation of metalaxyl and metalaxyl acid on Chiralcel OJ-H.[11] A semipreparative Chiralpak IC CSP was used in the resolution of more than 4 g of the proline analogs (*S*,*S*,*S*)- and (*R*,*R*,*R*)-2-methyloctahydroindole-2-carboxylic acids,[13] and Lux Cellulose CSP columns packed with 3 μm and 5 μm particle sizes were used in the enantioseparation of triazole fungicides.[6] Chiral separation of fenoterol for pharmacokinetic studies was described using a cellulose tris(3,5-dimethylphenylcarbamate)-coated silica gel CSP.[16]

The polysaccharide CSPs tris(3,5-dimethylphenylcarbamate) cellulose and amylose were used in the enantioseparation of substituted binaphthyls, and the separations were compared to those on β-cyclodextrin CSPs and new polymeric phases.[17] While the cellulose based CSP proved to be the most convenient in the chiral analyses, the polymeric CSPs showed

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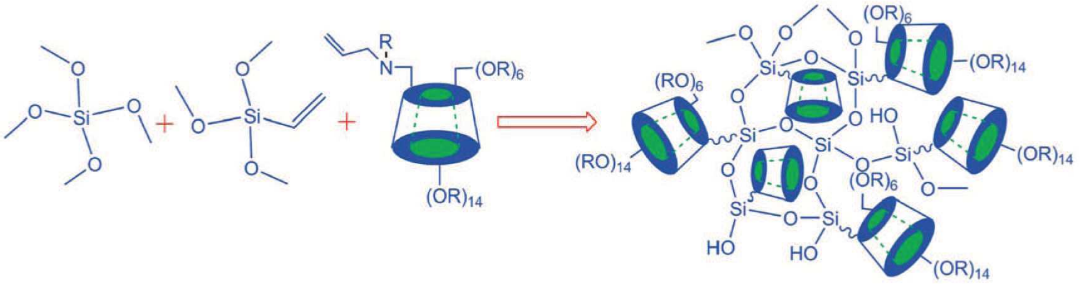


Figure 1. Schematic for the preparation of the perphenylcarbmoylated β-cyclodextrin—silica hybrid monolithic capillary column. Reprinted with permission from ref 20. Copyright 2011 American Chemical Society.

complementary separation behavior for some derivatives that were difficult to separate on other systems.

HPLC methods for the enantioseparation of lesatropane were developed using Chiralpak AD-H for a normal phase separation and Chiralpak AS-RH in a reversed phase method.[15] The chiral separation of hesperidin and naringin was accomplished on Chiralpak IC and Chiralpak IA,[18] and naproxcinod was enantioresolved on a Chiralpak AD-H CSP.[19]

Cyclodextrin CSPs and Mobile Phase Additives. The use of cyclodextrins, mainly as CSPs, accounts for over a fourth of all publications in chiral HPLC in this review period. Various applications using commercially available columns exist, as well as employing cyclodextrins as chiral additives in the mobile phase and also using recently developed novel cyclodextrin CSPs such as those using monolithic technology.

Monolithic stationary phases are finding increased use in separations due to their unique structure which leads to improved chromatographic performance. Monoliths are formed of a single piece of porous material rather than the particles used in most stationary phases, and the pore structure can be adjusted for permeability and fast mass transfer. A novel perphenylcarbamoylated β-cyclodextrin—silica hybrid monolithic column was prepared using a "one-pot" approach in the capillary and was used in the enantioseparation of 13 racemates.[20] Using a polymerization system composed of mostly organic solvent (MeOH, DMF), the authors were able to effectively use water insoluble hydrophobic monomers and β-cyclodextrin derivatives in their preparation of organic—silica hybrid monolithic columns in a "one-pot" process. Figure 1 shows the schematic for the preparation of the perphenylcarbmoylated β-cyclodextrin—silica hybrid monolithic capillary column. The authors note this is a general "one-pot" synthesis technique suitable to other β-cyclodextrin derivatives and hydrophobic monomers in preparing organic—silica hybrid monolithic columns.

A novel single isomer cyclodextrin CSP was prepared from (6-monoureido-6-monodeoxy) permethylated β-cyclodextrin and used in the chiral separation of coumarin derivative racemates.[21] The use of a single isomer derivative was found to be advantageous for batch to batch reproducibility of reactions. A novel ethylenediamine-β-cyclodextrin functionalized monolith was prepared and used in the enantioseparation of ibuprofen.[22] Three novel mono(6A-*N*-(ω-alkenylamino)-6A-deoxy)perphenylcarbamoylated β-cyclodextrin CSPs with different length spacers were prepared and tested using 10 model racemates including aromatic alcohols, flavanone compounds, amines, and nonprotolytic compounds under normal phase conditions.[23] Other novel CSPs included mono(6A-azido-6A-deoxy)-per(*p*-chlorophenylcarbamonylated) β-cyclodextrin, which was prepared using different pore sizes and particle sizes and evaluated for enantioselectivity for various racemates in both reversed and normal phase modes,[24] and cyclodextrin derivatives modified by R-configuration groups and evaluated for the enantioresolution of nitroaromatic alcohols.[25]

Ultrahigh pressure liquid chromatography has garnered much interest due to its potential for significantly reducing analysis time and system turnaround and is finding application in chiral separations as well. Ultrahigh pressure liquid chromatography was employed with perphenylcarbamoylated β-cyclodextrin on sub-1-μm mesoporous silica particles and was tested by the enantioseparation of six basic and neutral racemates.[26] This CSP had low back-pressure with a maximum flow rate of 2 mL/min and showed good enantioresolution of the test solutes.

Ultrahigh pressure chiral separations were also performed using chiral mobile phase additives rather than CSPs. Sub-2-μm particles and ultrahigh pressure liquid chromatography using α-, β-, and γ-cyclodextrin mobile phase additives were investigated for fast chiral separations of drugs.[27] However, this chiral mobile phase additive method suffered from broad peaks and reduced column lifetime, as well as the consuming large amounts of cyclodextrin, thus resulting in increased analysis cost. Successful use of a sulfated-β-cyclodextrin chiral selector in a nanoliquid chromatography method was reported for the enantiomeric separation of ofloxacin, and the method was validated for linearity, accuracy, and precision.[28] Eight 2-arylpropionic acid nonsteroidal anti-inflammatory drugs were enantioresolved using hydroxypropyl-β-cyclodextrin as the chiral mobile phase additive,[29] and a mixture of nonchiral crown ether and dimethyl-β-cyclodextrin in the mobile phase was used in the chiral separation of primary amino racemates including tyrosine and phenylalanine.[30]

Applications using cyclodextrin based CSPs are abundant in the literature. Examples include the chiral separation of (+)/(−)-catechin in human plasma after cocoa consumption on a permethylated-γ-cyclodextrin CSP,[31] the enantioresolution of dextromethorphan/levomethorphan and metabolites in plasma on a Chiral CD-Ph column,[32] and the analysis of hesperetin enantiomers in human urine after the ingestion of blood-orange juice on a phenyl-carbamate-propyl-β-cyclodextrin CSP.[33] Three cyclodextrin CSPs were studied for the enantioseparation of 19 β-lactams, with the permethylated β-cyclodextrin phase proving to be the most effective.[34] The enantioresolution of 15 4,5-disubstituted imidazoles was examined using several native and derivatized bonded cyclodextrin CSPs in HPLC and also using several cyclodextrin derivatives as chiral selectors in CE,[35] with the result that 14 of the 15 analytes were separated by HPLC and eight were separated using CE.

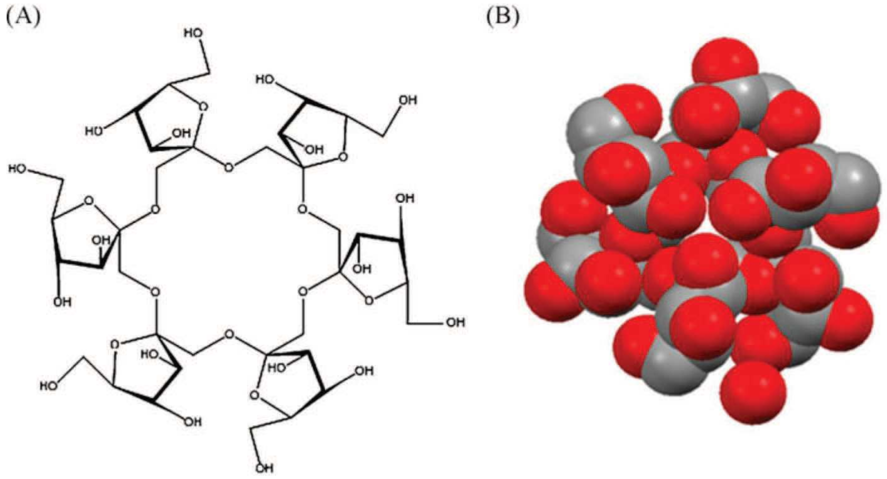


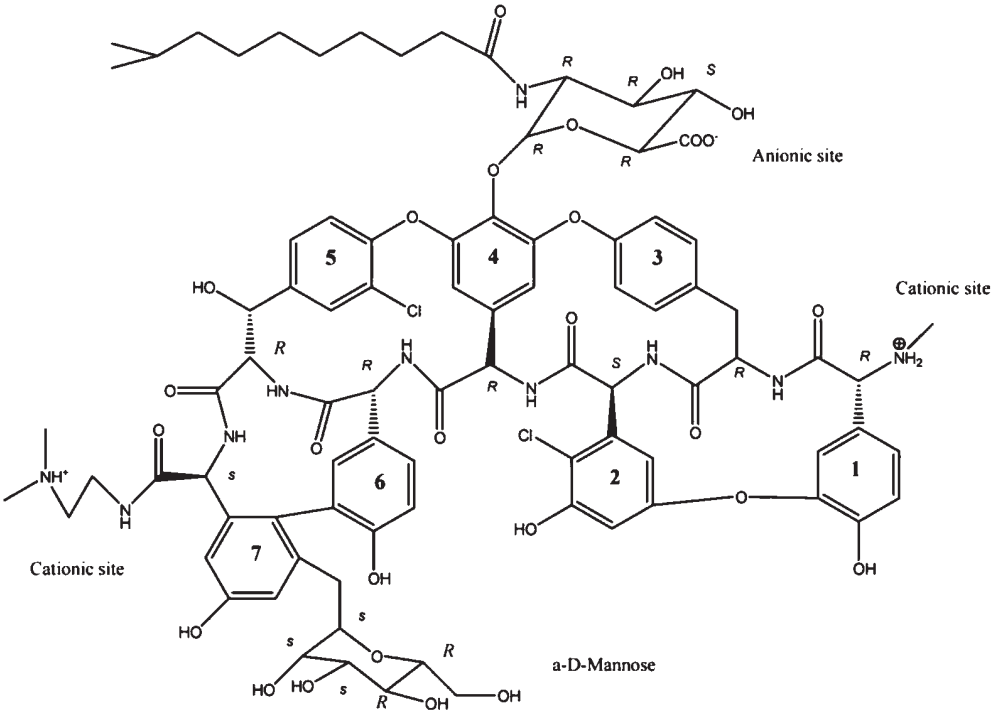
Figure 2. Structure of (A) cyclofructan 6 and (B) its spacefilling crystal structure. Reprinted with permission from ref 36, Effective enantiomeric separations of racemic primary amines by the isopropyl carbamate-cyclofructan6 chiral stationary phase. Copyright 2010 Elsevier B.V.

Cyclofructans. A relatively new class of CSPs are the various derivatized cyclofructans which seem to have great application potential. Figure 2 shows cyclofructan 6 and its spacefilling crystal structure, showing the crown ether core and fructofuran units.[36] A R-naphthylethyl functionalized cyclofructan 6 based CSP was used to separate racemates of substituted binaphthyl catalysts and was found to be more suitable for the enantioseparation of those solutes than a R-naphthylethyl β-cyclodextrin CSP.[37] An isopropyl-carbamate functionalized cyclofructan 6 CSP was evaluated by the attempted enantioseparation of 119 racemic amine-containing compounds, with 93% of the tested solutes enantioresolved, including some simple aliphatic amines with no other functional groups.[36] This isopropyl-carbamate functionalized cyclofructan 6 CSP was reported to be considered the most broadly applicable CSP for primary amine-containing analytes and works more effectively with organic solvents and supercritical fluids than current crown ether CSPs. A R-naphthylethyl-carbamate functionalized cyclofructan 6 CSP provided complementary selectivity for those solutes not resolved on the isopropyl-carbamate functionalized cyclofructan 6 CSP, so ultimately, 98% of the 119 amine-containing solutes attempted were enantioseparated.[36] An isopropyl-carbamate functionalized cyclofructan 6 CSP was also used in the direct enantioseparation of Betti base analogs, and the effects of mobile phase composition, nature and concentration of mobile phase modifiers, and structures of the analytes were reported.[38] A R-naphthylethyl functionalized cyclofructan 6 based CSP and a dimethylphenycarbamate cyclofructan 7 CSP were synthesized and evaluated in the enantioresolution of various classes of analytes.[39] Enantioselectivity was found to be complementary between the two CSPs, with the authors reporting that 43% of the test solute enantiomers were resolved. Classes of chiral compounds reported to be separated included acids, amines, metal complexes, and neutral compounds, and method development information was reported.[39]

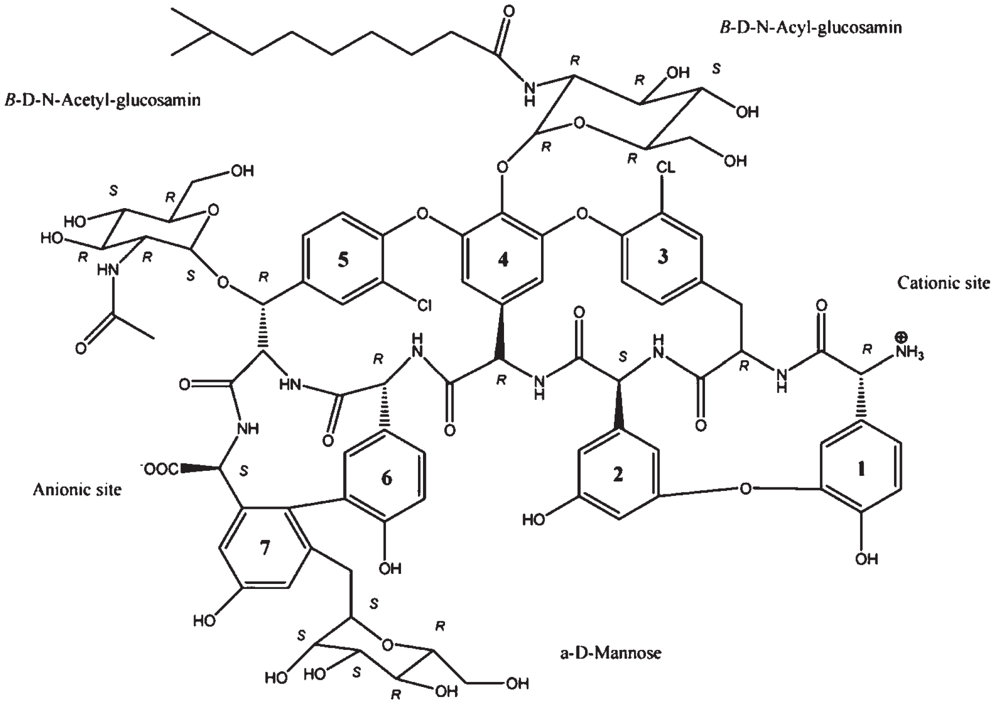
Macrocyclic Antibiotic CSPs. Though reports using macrocyclic antibiotic CSPs decreased in this review period, macrocyclic antibiotics continue to be developed and evaluated as chiral selectors. For example, dalbavancin, a macrocyclic antibiotic structurally related to teicoplanin, was used in the synthesis of two new CSPs which differed only in the binding chemistry.[40] Figure 3 shows the structure of dalbavancin and teicoplanin for comparison. These novel dalbavancin CSPs were evaluated relative to teicoplanin CSPs by comparing the enantioseparations of approximately 250 racemates using three different mobile phases.[40] The mobile phases included normal phase, polar organic phase, and reversed phase modes, and the tested analytes included heterocyclic compounds, chiral acids, chiral amines, chiral alcohols, chiral sulfoxides and sulfilimines, amino acids and amino acid derivatives, and other chiral compounds. The dalbavancin CSP was found to be complementary in selectivity compared to teicoplanin, with some compounds not separated on teicoplanin resolved on the dalbavanin CSP, but other compounds were enantioseparated only on the teicoplanin CSP.

Commercially available vancomycin and teicoplanin CSPs are used for many chiral separations in the literature in this review period. The commercially available vancomycin CSP Chirobiotic V column was used in a reverse polar ionic liquid chromatographic method for the enantioseparation of mirtazapine and its metabolite in rat plasma.[41] A method using the vancomycin based CSP Chirobiotic V2 was developed and evaluated for the enantioseparation of atenolol. Teicoplanin (Chirobiotic T and T2) and teicoplanin aglycone (Chirobiotic TAG) were used as chiral selectors in the direct chiral resolution of monoterpene based 2-amino carboxylic acids,[42] and macrocyclic glycopeptide based CSPs were successfully used in the enantioseparation of three underivatized γ-amino acids.[43]

Ligand Exchange CSPs. Ligand exchange CSPs were used in several applications during this review period. For example, the simultaneous analysis of aspartame and its hydrolysis products in soda pop was accomplished by a two-dimensional HPLC system using a ligand exchange CSP for the enantioseparation of amino acid enantiomers,[44] and the chiral separation of ofloxacin was achieved using chiral ionic liquid-assisted ligand exchange chromatography.[45] A study was reported on the enantioresolution of pirinixic acid derivatives on *tert*-butylcarbamoylquinine and quinine based chiral anion exchange CSPs[46] and found that the elution order of some derivatives changed when compared to separations of the derivatives on amylose tris(3,5-dimethylphenylcarbamate) CSPs. A 1,2,3-triazolo-linked quinine *tert*-butyl carbamate anion exchange CSP showed enhanced enantioselectivity for mandelic acids and their derivatives, with the



The structure of the macrocyclic glycopeptide dalbavancin.



The structure of the macrocyclic glycopeptide teicoplanin.

Figure 3. Structures of the macrocyclic glycopeptides dalbavancin and teicoplanin. Reprinted with permission from ref 40. Copyright 2010 John Wiley & Sons, Inc.

authors suggesting that the rigid 1,2,3-triazole group participates in the formation of an enantioselective-binding pocket.[47]

Protein Based CSPs. Protein based enantioseparations, a well-established group of CSPs, comprised around ten percent of HPLC chiral separations. While most articles report applications using commercially available CSPs, novel stationary phases and strategies for method development are also being developed. A new kind of immobilized human serum albumin CSP was

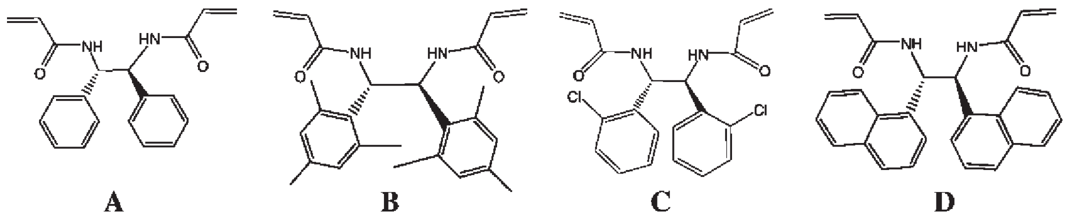


Figure 4. Structures of (A) the monomeric units used in the synthesis of the commercial P-CAP-DP CSP and (B, C, and D) the three new polymeric phases. Reprinted with permission from ref 56, Synthesis and chromatographic evaluation of new polymeric chiral stationary phases based on three (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine derivatives in HPLC SFC, Figure 1. Copyright 2011 Springer.

developed on the basis of a high-performance affinity monolith and was used for the chiral separation of amino acids in urine.[48] The analysis was found to be relatively rapid and was also employed in the measurement of the enzyme catalytic activity in the incubation of D,L-amino acids with D-amino acid oxidase and the study of the enzyme kinetics. A generalized method development screening procedure that allows LC-MS compatibility was reported by Michishita et al.[49] Applications developed using protein based CSPs included enantioseparations of doxazosin on an ovomucoid column,[50] dorzolamide hydrochloride on α-1-acid glycoprotein CSP,[51] and aryloxyphenoxypropionic herbicides in soil on α-1-acid glycoprotein CSP.[52]

Miscellaneous. Other novel CSPs for HPLC that were reported and studied during this review period include polymeric phases, proline based phases, and 4-(3,5-dinitrobenzamido)-tetrahydrophenanthrene phases. Three new polymeric CSPs were synthesized on the basis of three (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine derivatives and evaluated for use in normal phase HPLC and supercritical fluid chromatography (SFC). These phases were also compared with the commercially available P-CAP-DP polymeric CSP.[53] Figure 4 illustrates the structures of the 1,2 diphenyl-1,2-ethanediyl bis-2-propen amide monomeric units used in the synthesis of the commercial P-CAP-DP CSP and the three new polymeric phases. These CSPs are composed of a thin polymer layer chemically bonded to silica gel. One advantage of these phases is that they may be manufactured in the *R*,*R* or *S*,*S* form to reverse the order of elution using the same mobile phase. The novel CSPs showed similar or better enantioselectivities in both HPLC and SFC than the commercial column and also achieved faster separations.

The commercially available polymeric CSPs P-CAP, P-CAP-DP, and DEAVB, 9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid bis-4-vinylphenyl amide, were evaluated for the enantiomeric resolution of 17 chiral sulfoxides, with the DEABV CSP separations reported to be superior.[54] Reversed phase enantioseparations on these columns were also reported for the first time.[54]

A novel doubly tethered diproline CSP was used in a study of the effect of temperature on enantioselectivity and robustness of separation of enantiomers including 1,1′-bi-2-naphthol and warfarin,[55] and unusual peak profiles of warfarin were characterized on two oligoproline CSPs.[57] Eight diproline CSPs with different end-capping groups were synthesized and evaluated for the chiral resolution of 41 racemic analytes, with the enantioselectivity increasing with increasing steric bulkiness near the N-terminal of diproline.[58]

A CSP derived from 4-(3,5-dinitrobenzamido)tetrahydrophenanthrene was used in the enantioresolution of mandelic acid and its analogs, with suggested chiral recognition models also presented.[59] Chiral resolution of thalidomide and its derivatives in water sediment was achieved on a Ceramosphere RU-2 CSP which employs a chiral ruthenium complex trapped in a zeolite structure.[60] This CSP was used in a study of supramolecular dynamics. A crown ether tetracarboxylic acid CSP, Chirosil RCA(+), was used in the enantioseparation of aromatic amines and aromatic amino alcohols, with a discussion of the relationship between retention, enantioselectivity, and molecular structure.[61] MIPs of affinity polymeric materials were synthesized for the first time in supercritical carbon dioxide and tested as CSPs in the enantioseparation of racemic tryptophan.[62]

■ CAPILLARY ELECTROPHORESIS

Capillary electrophoresis (CE) has perceived advantages over LC techniques in its reduced time of analysis, lower amounts of mobile phase and buffers required, and use of a wide variety of chiral mobile phase additives. CE techniques comprised about a fourth of all chiral separations during this review period. Separations using cyclodextrins and micellar separations comprised the bulk of the CE enantioseparations, about two-thirds. Publications involving techniques using ligand exchange CE accounted for around ten percent of all chiral CE articles, and various miscellaneous techniques accounted for the remaining CE enantioseparations in this review period.

Cyclodextrins. Chiral separations using cyclodextrins and their derivatives as chiral selectors comprise a majority of chiral CE separations in this review period, illustrating their versatility and usefulness. Advantages of cyclodextrins and their derivatives include their water solubility, stability in solution, UV transparency, and ionizability. The enantioseparation of cis-β-lactams was studied using carboxylmethyl α-, β-, and γ-cyclodextrins, as well as sulfobutyl β-cyclodextrin derivatives as chiral selectors.[63] These derivatives along with neutral β-cyclodextrins were also used in dual cyclodextrin systems, and 19 cis-β-lactams were enantioresolved. Other examples of the use of cyclodextrin derivatives in CE include the investigation of neutral and negatively charged cyclodextrins for the enantioseparation of antimalarial drugs. Carboxymethyl-β-cyclodextrin resulted in the best separation of primaquine from quinocide with the simultaneous complete resolution of both compounds.[64] The enantioseparation of three vinca alkaloids was investigated using an aqueous CE system using native α-, β-, and γ-cyclodextrins and their hydroxypropylated, randomly methylated, carboxymethylated, and sulfobutylated derivatives, with the successful enantioresolution of all three analytes.[65] Carboxymethylated-β-cyclodextrin was used as the chiral selector in an electrokinetic chromatography study of zopiclone enantioselective binding to human albumin and plasma proteins.[66]

Six tetrahydronaphthalenic derivatives were successfully enantioresolved using CE and a dual system of highly sulfated-β-cyclodextrin and γ-cyclodextrin.[67] A dual system of chiral selectors using heptakis(2,3-di-*O*-acetyl-6-*O*-sulfo)-β-cyclodextrin and heptakis(2,3-di-*O*-methyl-6-*O*-sulfo)-β-cyclodextrin was used in the enantioseparation of oxfendazole.[68] The enantiomers of ofloxacin and ornidazole in pharmaceutical formulations was achieved by CE using sulfated β-cyclodextrin as a chiral selector,[69] and a separation mechanism was proposed to account for the remarkable enantioselectivity of mixtures of highly sulfated β-cyclodextrins compared with single isomers in capillary zone electrophoresis.[70]

A CE partial-filling technique using hydroxypropyl—β-cyclodextrin as the chiral selector for the enantioresolution of pheniramine was described,[71] and the enantiomers of two acylamine fungicides were separated by electrokinetic chromatography using succinyl derivatized cyclodextrins.[72] Other novel cyclodextrin derivatives found use in chiral CE separations, including a novel single isomer mono-6-deoxy-6-((2*S*,3*S*)-(+)-2,3-*O*-isopropylidene-1,4-tetramethylenediamine-β-cyclodextrin, which was synthesized and studied in the enantioseparation of 10 dansyl-amino acids and *N*-acetylphenylalanine, showing very good chiral recognition ability.[73]

Micelles. The use of micellar electrokinetic chromatography (MEKC) for chiral separations showed a slight increase in usage during this review period. Cyclodextrin based chiral selectors continue to dominate the MEKC separations. The enantioseparation of four chiral polycyclic musks was achieved for the individual musks using cyclodextrin and SDS as surfactant, and a dual cyclodextrin system containing two neutral cyclodextrins was used in a MEKC method for the simultaneous enantioresolution of 3 of the 4 musks.[74] Hydroxypropyl-β-cyclodextrin and SDS were used in the chiral separation of three chiral triazole fungicides, hexaconazole, penconazole, and myclobutanil, and two online preconcentration methods, stacking with a reverse migrating micelle and sweeping, were evaluated with the sweeping method proving superior.[75] The enantioseparation of dipeptides was achieved using a precolumn derivatization procedure then resolving using a hydroxypropyl-β-cyclodextrin MEKC method.[76] Another cyclodextrin-modified MEKC method used hydroxypropyl-γ-cyclodextrin for the enantioseparation of econazole.[77] The synthetic pyrethroid *cis*-bifenthrin was enantioresolved using heptakis (2,3,6-tri-*O*-methyl)-β-cyclodextrin, and the method was applied to commercial insecticide formulations.[78] A polymer/β-cyclodextrin assembling molecular film modified capillary was used in a MEKC method for the separation of cis—trans isomers and enantiomers of sertraline.[79]

Polymeric surfactants continue to find use in chiral MEKC separations. For example, polysodium *N*-undecenoxycarbonyl-L-isoleucinate was determined to be the best chiral selector in the enantioseparation of three chiral barbiturates, mephobarbital, pentobarbital, and secobarbital.[80] Mixed molecular micelles formed using the polymeric chiral surfactants polysodium *N*-undecenoxycarbonyl-L-isoleucinate and polysodium *N*-undecenoyl-L,L-leucylvalinate were used in the MEKC/atmospheric pressure photoionization MS method for the chiral separation of benzoin derivatives.[81]

The novel chiral selector clindamycin phosphate, a lincosamide antibiotic, was evaluated for enantioseparation capability toward basic drugs by MEKC, with excellent separation of enantiomers of nefopam, citalopram, tryptophan, chlorphenamine, propranolol, and metoprolol.[82] A water-insoluble solid compound, di-*t*-butyl L-tartrate, was used as an oil to prepare a microemulsion used in the MEKC method for the enantioresolution of β-blockers and structurally related compounds.[83] Sodium cholate was used in the chiral MEKC separation of amygdalin and neoamygdalin.[84]

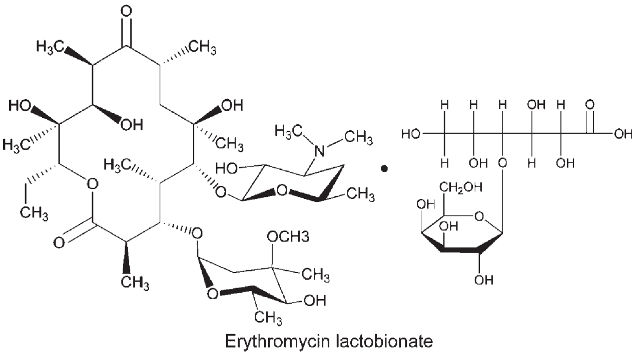


Figure 5. Structure of erythromycin lactobionate. Reprinted with permission from ref 88. Copyright 2010 John Wiley & Sons, Inc.

Ligand Exchange. Ligand exchange CE remains an established technique, comprising about ten percent of all chiral CE separations during this review period. Novel chiral ligands continue to be developed. A new family of copper β-amino alcohol ligand exchange selectors was developed for the chiral separation of dansyl amino acids, unmodified amino acids, and propranolol by capillary zone electrophoresis.[85] Another example of a novel chiral ligand exchange selector was Zn(II)-L-prolinamide, used in a pharmacokinetic study of sodium benzoate based on its inhibitoryactivity in the D-amino acid oxidase mediated oxidation of D-serine.[86] D-Quinic acid was used as the chiral selector ligand and Fe(III), Co(II), Ni(II), Cu(II), and Zn(II) ions were used in the enantioresolution of DL-isocitric acid.[87]

Miscellaneous. A wide variety of chiral selectors have been used in CE, and one of the recently reported new chiral selectors is the macrolide antibiotic erythromycin lactobionate, used in a nonaqueous media CE separation of the basic drugs propranolol hydrochloride and duloxetine.[88] The structure of erythromycin lactobionate is shown in Figure 5. Erythromycin lactobionate was reported to have high solubility and low viscosity in the methanol solvent, as well as very weak UV absorption. Another macrolide antibiotic, clarithromycin lactobionate, was investigated for its potential in the enantiomeric separation by CE of several basic drugs, including metoprolol, atenolol, propranolol, bisoprolol, esmolol, ritodrine, and amlodipine.[89] A new chiral selector, sodium arsenyl-(L)-(+) tartrate was introduced for CE and evaluated by enantioseparations of many cationic analytes including primary, secondary, and tertiary amines.[90]

Highly succinate-substituted α-cyclosophoro-octadecaoses, containing 18 glucose units per ring as the predominant form, were successfully used as chiral additives in CE for the separation of five flavanones and flavanone-7-*O*-glycosides, while unsubstituted α-cyclosophoro-octadecaoses did not give effective enantioresolution.[91] A linear polysaccharide, maltodextrin, was used in the CE method for the enantioseparation of cetirizine and hydroxyzine in human plasma.[92] The linear ionic polysaccharide chondroitin sulfate A was used as chiral selector in an affinity electrokinetic chromatography method for the enantiomeric separation of nefopam hydrochloride.[93]

An ephedrine based ionic liquid served as both chiral selector and background electrolyte in the nonaqueous CE enantioseparation of rabeprazole and omeprazole.[94] The chiral selectivity of guanosine gels in CE was examined,[95] and a microchip affinity electrophoresis method using bovine serum albumin gave a good chiral separation of amino acids.[96]

■ CAPILLARY ELECTROCHROMATOGRAPHY

Capillary electrochromatography (CEC) remains a powerful analytical chiral separation technique. CEC while similar to CE in that the mobile phase is driven by electroosmosis, differs significantly from CE in that the separating mechanism is the partition between the liquid and stationary phases. Molecular imprinted polymer (MIP) based chiral separations continue to comprise a large number of all CEC enantioseparations. An advantage of MIP based enantioseparations is the unambiguous elution order of enantiomeric pairs due to the MIP's predetermined selectivity. A powerful generalized procedure for the preparation of open tubular MIP chiral capillary columns was reported by Zaidi et al.[97] In the first study, the preparation of the MIP columns was identical in every respect except for the identity of the chiral template, which was composed of compounds containing acidic functional groups including ibuprofen, naproxen, mandelic acid, and others. While optimizing chromatographic conditions improved resolution on the different MIP columns, a universal eluent was also used with satisfactory results. This generalized MIP procedure was also used to prepare open tubular capillary columns with basic functional group templates.[98] These basic compounds included atenolol, sulpiride, methyl benzylamine, and (1-naphthyl)-ethylamine, with the chiral separation of atenolol and sulpiride found to be better than or comparable to non-MIP separations and other MIP based techniques. Another study applied the generalized procedure to templates consisting of phenyl carboxylic acids and their derivatives.[99] While enantioresolution was achieved for these template enantiomers, the separation performances were found to be inferior to those for the MIP columns produced for the Profen drugs. This generalized procedure appears to have broad application in the production of MIP based CSPs.

A monolithic MIP column was prepared using (−)-norepinephrine as the template and used in the enantioresolution of neurotransmitters including dopamine, epinephrine, isoproterenol, norepinephrine, octopamine, and synephrine.[100] (*S*)-Ornidazole was used as the template molecule for a MIP monolithic column used in the fast separation of ornidazole by pressurized CEC.[101] The application to similar antiparasitic drugs was also investigated, with the results indicating that secnidazole could also be enantioresolved.

The high specificity of MIP based chiral separations is advantageous, although pure enantiomers must be available as templates to construct the CSP. Monolithic columns based on cyclodextrin derivatives have also been constructed in this review period, with apparently more universal use in the separation of various mixtures of racemates. A series of monolithic capillary columns were prepared by chemically graphing β-cyclodextrin and derivatives to the surface of monoliths.[102] The cyclodextrin derivatives included aspartate-β-cyclodextrin, NH_2-β-cyclodextrin, and hydroxylpropyl-β-cyclodextrin. These CSPs were used in the CEC separation of racemic mixtures of eight amino acids and the chiral drugs mexiletine hydrochloride and oxybutynin chloride in human plasma, with good selectivity shown. Another article reported the synthesis of a sulfated poly-β-cyclodextrin-modified silica based monolithic column which was found to resolve the tedious desalting procedure necessary when sulfated cyclodextrins are used as chiral additives.[103]

New nanomaterials derived from chitosan and cross-linked with polyacrylamide were used as the CSP for open-tubular CEC and were investigated for use in enantioseparations.[104] However, only two groups of α-tocopherol stereoisomers were resolved on this new CSP. Another new CSP based on ligand exchange continuous bed technology was prepared using L-prolinamide as the chiral selector[105] and used in the enantioseparation of amino acids and α-hydroxy acids. Another continuous bed containing L-4-hydroxyproline as the chiral selector showed the possibility of simultaneous enantioseparation of amino acids and α-hydroxy acids.[105]

■ GAS CHROMATOGRAPHY

Gas chromatography (GC) remains a popular technique in this review period. Cyclodextrin derivatives have dominated the field of chiral separation in GC. A novel and promising CSP for GC used ionic liquids to dissolve ionic cyclodextrin derivatives.[106] Ionic liquids have emerged as important stationary phases for GC due to the fact that they are fairly nonvolatile, possess a rather large range of thermal stability, and have a variety of physical and chemical properties. One concern from previous work was the reported reduction in the range of enantioselectivity when the CSP was composed of neutral cyclodextrins dissolved in ionic liquid. However, the use of charged cyclodextrins as the chiral selectors has resulted in significantly increased enantioselectivity and efficiencies. A variety of chiral molecules were resolved, and the performance of these novel ionic liquid/ionic cyclodextrin CSPs was found to be comparable and complementary to commercially available cyclodextrin CSPs. There appears a growing interest in ionic liquid and ionic cyclodextrin CSPs, as demonstrated by the numerous citations of this article.

There has also been interest in the use of derivatized cyclofructan CSPs in GC chiral separations. These novel chiral selectors, first introduced in 2010, have been evaluated in the enantioseparation of esters, β-lactams, alcohols, amino alcohols, tartrates, and amino acid derivatives.[107,108] Evaluation of the separation mechanism indicated that there was no inclusion complex formed. A different type of CSP for GC, chiral metal−organic framework coated open tubular columns, was reported by Xie et al.[109] and evaluated for enantioselectivity toward aldehydes, ketones, organic acids, amino acids, and alcohols.

Commercially available GC CSPs also were utilized extensively during this review period. For example, the simultaneous enantioseparation of methylamphetamine, ephedrine, and pseudoephedrine derivatives was accomplished on a γ-cyclodextrin Chiraldex G-PN CSP coupled to mass spectrometry.[110] A beta-DEX cyclodextrin column was used in the development of a method for optically active food flavor chemicals menthol, menthyl acetate, borneol, perillaldehyde, and 1,8-cineol.[111] The enantiomeric resolution of amino acids for space exploration missions was evaluated using a Chirasil-I-Val CSP in two GC/MS methods.[112]

■ SUPERCRITICAL FLUID CHROMATOGRAPHY

Supercritical fluid chromatography (SFC) found increased use during this review period, with both novel CSPs and applications on commercial CSPs in the literature. Three new polymeric CSPs structurally related to (1*S*,2*S*)-1,2-diphenylethylenediamine, the monomer used in the commercially available P-CAP-DP polymeric CSPs, were synthesized and evaluated in HPLC and SFC.[56] These novel polymeric CSPS showed similar or better enantioselectivities than the commercial columns and were found to have faster separation times.

SIMULATED MOVING BED CHROMATOGRAPHY

Simulated moving bed chromatography (SMB) continues to find use in preparative scale chiral separations. A two-column, semicontinuous, open-loop SMB system was used in the chiral separation of reboxetine racemate.[113] Flurbiprofen enantiomers were separated by SMB using Chiralpak AD CSP,[114] and (*RS*,*RS*)-2-(2,4-difluorophenyl)butane-1,2,3-triol was subjected to chiral separation using intermittent SMB.[115]

MISCELLANEOUS TECHNIQUES

High-Speed Counter-Current Chromatography. Enantiomeric separation by high-speed counter-current chromatography (HSCCC) has shown increased activity in the field with an increase in the number of publications from the last review period. A brief review of the literature showed that the preponderance of applications used cyclodextrin derivatives as chiral selectors. For example, sulfated-β-cyclodextrin was used in the enantioseparation of lomefloxacin hydrochloride,[116] while hydroxypropyl-β-cyclodextrin was the chiral selector in the chiral resolution of phenylsuccinic acid[117] and (*R*,*S*)-naproxen.[118] An interesting biphasic chiral recognition method utilized two chiral selectors, one in the aqueous phase and a different one in the organic stationary phase, in which the chiral selectors showed affinity for the opposite enantiomers of the analyte.[119] The biphasic system showed much more efficiency in the chiral separation of α-cyclohexylmandelic acid than traditional monophasic recognition enantioseparation since both lipophilic and hydrophilic chiral selectors participated in the resolution.

Thin Layer Chromatography. Thin layer chromatography use for chiral separations did not have a significant presence in the literature during this review period.

CONCLUSIONS

The field of chiral separations has reached a clear level of maturity after approximately 30 years of development since the first successful commercialized columns appeared on the market. Several areas that should experience increased interest in the coming years will be development of monolithic CSPs, ionic-liquid phases, and derivatized cyclodextrin phases. Chiral separation's importance to so many diverse and critical industries such as the pharmaceutical, agrochemical, petrochemical, and food industry ensures future use and development.

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REFERENCES

(1) Musshoff, F.; Madea, B.; Stuber, F.; Stamer, U. M. *J. Anal. Toxicol.* **2010**, *34*, 581–586.

(2) Vyas, S.; Patel, A.; Ladva, K. D.; Joshi, H. S.; Bapodra, A. H. *J. Pharm. Bioallied Sci.* **2011**, *3*, 310–314.

(3) Avula, B.; Khan, S. I.; Tekwani, B. L.; Dhammika Nanayakkara, N. P.; McChesney, J. D.; Walker, L. A.; Khan, I. A. *Biomed. Chromatogr.* **2011**, *25*, 1010–1017.

(4) Zhang, K.; Xue, N.; Shi, X.; Liu, W.; Meng, J.; Du, Y. *J. Pharm. Biomed. Anal.* **2011**, *55*, 220–224.

(5) Gowramma, B.; Muralidharan, S.; Babu, B.; Meyyanathan, S. N.; Elango, K.; Suresh, B. *J. Pharm. Res.* **2011**, *4*, 1617–1619.

(6) Qiu, J.; Dai, S.; Zheng, C.; Yang, S.; Chai, T.; Bie, M. *Chirality* **2011**, *23*, 479–486.

(7) Ali, I.; Al-Othman, Z.; Hussain, A.; Saleem, K.; Aboul-Enein, H. *Chromatographia* **2011**, *73*, 251–256.

(8) Ilisz, I.; Pataj, Z.; Berkecz, R.; Szatmari, I.; Fueloep, F.; Peter, A. *J. Chromatogr., A* **2010**, *1217*, 2980–2985.

(9) Pataj, Z.; Ilisz, I.; Berkecz, R.; Forro, E.; Fueloep, F.; Peter, A. *Chirality* **2010**, *22*, 120–128.

(10) Zhang, A.; Xie, X.; Liu, W. *J. Agric. Food Chem.* **2011**, *59*, 4300–4305.

(11) Zhang, X.; Xia, T.; Chen, J.; Huang, L.; Cai, X. *J. Agric. Food Chem.* **2010**, *58*, 5004–5010.

(12) Rao, R. N.; Maurya, P. K.; Shinde, D. D. *Biomed. Chromatogr.* **2010**, *24*, 1228–1233.

(13) Sayago, F. J.; Pueyo, M. J.; Calaza, M. I.; Jimenez, A. I.; Cativiela, C. *Chirality* **2011**, *23*, 507–513.

(14) Mone, M. K.; Chandrasekhar, K. B. *J. Pharm. Biomed. Anal.* **2011**, *54*, 248–251.

(15) Yang, L.; Xie, Y.; Gu, Z.; Wang, A.; Chen, H.; Lu, Y. *Chirality* **2011**, *23*, 581–584.

(16) Ullrich, T.; Wesenberg, D.; Bleuel, C.; Krauss, G.; Schmid, M.; Weiss, M.; Guebitz, G. *Biomed. Chromatogr.* **2010**, *24*, 1125–1129.

(17) Loukotkova, L.; Tesarova, E.; Bosakova, Z.; Repko, P.; Armstrong, D. *J. Sep. Sci.* **2010**, *33*, 1244–1254.

(18) Belboukhari, N.; Cheriti, A.; Roussel, C.; Vanthuyne, N. *Nat. Prod. Res.* **2010**, *24*, 669–681.

(19) Sun, J.; Liu, J.; Tu, W.; Xu, C. *Chemosphere* **2010**, *81*, 1308–1313.

(20) Zhang, Z.; Wu, M.; Wu, R.; Dong, J.; Ou, J.; Zou, H. *Anal. Chem.* **2011**, *83*, 3616–3622.

(21) Varga, G.; Tarkanyi, G.; Nemeth, K.; Ivanyi, R.; Jicsinszky, L.; Toke, O.; Visy, J.; Szente, L.; Szeman, J.; Simonyi, M. *J. Pharm. Biomed. Anal.* **2010**, *51*, 84–89.

(22) Lv, Y.; Mei, D.; Pan, X.; Tan, T. *J. Chromatogr., B* **2010**, *878*, 2461–2464.

(23) Lai, X.; Tang, W.; Ng, S. *J. Chromatogr., A* **2011**, *1218*, 3496–3501.

(24) Qin, Q.; Zhang, S.; Zhang, W.; Zhang, Z.; Xiong, Y.; Guo, Z.; Fan, J.; Sheng, R.; Finlow, D.; Yin, Y. *J. Sep. Sci.* **2010**, *33*, 2582–2589.

(25) Li, X.; Zhou, Z.; Xu, D.; Zhang, J. *Talanta* **2011**, *84*, 1080–1092.

(26) Ai, F.; Li, L.; Ng, S.; Tan, T.; Thatt, Y. *J. Chromatogr., A* **2010**, *1217*, 7502–7506.

(27) Guillarme, D.; Bonvin, G.; Badoud, F.; Schappler, J.; Rudaz, S.; Veuthey, J. *Chirality* **2010**, *22*, 320–330.

(28) Rosales-Conrado, N.; Leon-Gonzalez, M.; Rocco, A.; Fanali, S. *Curr. Anal. Chem.* **2010**, *6*, 209–216.

(29) Ye, J.; Yu, W.; Chen, G.; Shen, Z.; Zhen, S. *Biomed. Chromatogr.* **2010**, *24*, 799–807.

(30) Zhang, C.; Huang, W.; Chen, Z.; Rustum, A. *J. Chromatogr., A* **2010**, *1217*, 4965–4970.

(31) Ritter, C.; Zimmermann, B.; Galensa, R. *Anal. Bioanal. Chem.* **2010**, *397*, 723–730.

(32) Kikura-Hanajiri, R.; Kawamura, M.; Miyajima, A.; Sunouchi, M.; Goda, Y. *Anal. Bioanal. Chem.* **2011**, *400*, 165–174.

(33) Si-Ahmed, K.; Tazerouti, F.; Badjah-Hadj-Ahmed, Y.; Aturki, Z.; D'Orazio, G.; Rocco, A.; Fanali, S. *J. Pharm. Biomed. Anal.* **2010**, *51*, 225–229.

(34) Fodor, G.; Ilisz, I.; Szeman, J.; Ivanyi, R.; Szente, L.; Varga, G.; Forro, E.; Fueloep, F.; Peter, A. *Chromatographia* **2010**, *71*, S29–S34.

(35) Breitbach, Z.; Feng, Q.; Koswatta, P.; Dodbiba, E.; Lovely, C.; Armstrong, D. *Supramol. Chem.* **2010**, *22*, 758–767.

(36) Sun, P.; Armstrong, D. *J. Chromatogr., A* **2010**, *1217*, 4904–4918.

(37) Kalikova, K.; Janeckova, L.; Armstrong, D.; Tesarova, E. *J. Chromatogr., A* **2011**, *1218*, 1393–1398.

(38) Aranyi, A.; Ilisz, I.; Pataj, Z.; Szatmari, I.; Fulop, F.; Armstrong, D.; Peter, A. *Chirality* **2011**, *23*, 549–556.

(39) Sun, P.; Wang, C.; Padivitage, N.; Nanayakkara, Y.; Perera, S.; Qiu, H.; Zhang, Y.; Armstrong, D. *Analyst* **2011**, *136*, 787–800.

(40) Zhang, X.; Bao, Y.; Huang, K.; Barnett-Rundlett, K.; Armstrong, D. *Chirality* **2010**, *22*, 495–513.

(41) Rao, R. N.; Kumar, K.; Ramakrishna, S. *J. Chromatogr., B* **2011**, *879*, 1911–1916.

(42) Sipos, L.; Ilisz, I.; Pataj, Z.; Szakonyi, Z.; Fulop, F.; Armstrong, D.; Peter, A. *J. Chromatogr., A* **2010**, *1217*, 6956–6963.

(43) Pataj, Z.; Ilisz, I.; Aranyi, A.; Forro, E.; Fueloep, F.; Armstrong, D.; Peter, A. *Chromatographia* **2010**, *71*, S13–S19.

(44) Cheng, C.; Wu, S. *J. Chromatogr., A* **2011**, *1218*, 2976–2983.

(45) Bi, W.; Tian, M.; Row, K. *Analyst* **2011**, *136*, 379–387.

(46) Lammerhofer, M.; Pell, R.; Mahut, M.; Richter, M.; Schiesel, S.; Zettl, H.; Dittrich, M.; Schubert-Zsilavecz, M.; Lindner, W. *J. Chromatogr., A* **2010**, *1217*, 1033–1040.

(47) Kacprzak, K.; Maier, N.; Lindner, W. *J. Sep. Sci.* **2010**, *33*, 2590–2598.

(48) Yao, C.; Qi, L.; Qiao, J.; Zhang, H.; Wang, F.; Chen, Y.; Yang, G. *Talanta* **2010**, *82*, 1332–1337.

(49) Michishita, T.; Franco, P.; Zhang, T. *J. Sep. Sci.* **2010**, *33*, 3627–3637.

(50) Liu, K.; Zhong, D.; Chen, X. *J. Chromatogr., B* **2010**, *878*, 2415–2420.

(51) Shamsipur, M.; Heydari, R.; Jamasbi, E. S.; Abdollahpour, A. *J. Sep. Sci.* **2010**, *33*, 2328–2333.

(52) Guillen-Casla, V.; Magro-Moral, J.; Rosales-Conrado, N.; Perez-Arribas, L. V.; Leon-Gonzalez, M. E.; Polo-Diez, L. M. *Anal. Bioanal. Chem.* **2011**, *400*, 3547–3560.

(53) Payagala, T.; Wanigasekara, E.; Armstrong, D. W. *Anal. Bioanal. Chem.* **2011**, *399*, 2445–2461.

(54) Lourenco, T. C.; Armstrong, D. W.; Cass, Q. B. *Chromatographia* **2010**, *71*, 361–372.

(55) Lao, W.; Gan, J. *J. Sep. Sci.* **2010**, *33*, 3052–3059.

(56) Payagala, T.; Wanigasekara, E.; Armstrong, D. *Anal. Bioanal. Chem.* **2011**, *399*, 2445–2461.

(57) Lao, W.; Gan, J. *J. Chromatogr., A* **2010**, *1217*, 6545–6554.

(58) Dai, Z.; Ye, G.; Pittman, C., Jr.; Li, T. *J. Chromatogr., A* **2011**, *1218*, 5498–5503.

(59) Aneja, R.; Luthra, P. M.; Ahuja, S. *Chirality* **2010**, *22*, 479–485.

(60) Ali, I.; Gupta, V. K.; Aboul-Enein, H. *Chirality* **2010**, *22*, 416–424.

(61) Shen, S.; Ma, S.; Lee, H.; Manolescu, C.; Grinberg, M.; Yee, N.; Senanayake, C.; Grinberg, N. *J. Liq. Chromatogr. Relat. Technol.* **2010**, *33*, 153–166.

(62) da Silva Mara, S.; Vao Eva, R.; Temtem, M.; Mafra, L.; Caldeira, J.; Aguiar-Ricardo, A.; Casimiro, T. *Biosens. Bioelectron.* **2010**, *25*, 1742–1747.

(63) Nemeth, K.; Varga, E.; Ivanyi, R.; Szeman, J.; Visy, J.; Jicsinszky, L.; Szente, L.; Forro, E.; Fulop, F.; Peter, A. *J. Pharm. Biomed. Anal.* **2010**, *53*, 382–388.

(64) Nemeth, K.; Tarkanyi, G.; Varga, E.; Imre, T.; Mizsei, R.; Ivanyi, R.; Visy, J.; Szeman, J.; Jicsinszky, L.; Szente, L. *J. Pharm. Biomed. Anal.* **2011**, *54*, 475–481.

(65) Sohajda, T.; Varga, E.; Ivanyi, R.; Fejos, I.; Szente, L.; Noszal, B.; Beni, S. *J. Pharm. Biomed. Anal.* **2010**, *53*, 1258–1266.

(66) Asensi-Bernardi, L.; Martin-Biosca, Y.; Medina-Hernandez, M.; Sagrado, S. *J. Chromatogr., A* **2011**, *1218*, 3111–3117.

(67) Lipka, E.; Danel, C.; Yous, S.; Bonte, J.; Vaccher, C. *Electrophoresis* **2010**, *31*, 1529–1532.

(68) Rousseau, A.; Gillotin, F.; Chiap, P.; Crommen, J.; Fillet, M.; Servais, A. *Electrophoresis* **2010**, *31*, 1482–1487.

(69) Al Azzam, K.; Saad, B.; Adnan, R.; Aboul-Enein, H. *Anal. Chim. Acta* **2010**, *674*, 249–255.

(70) Dubsky, P.; Svobodova, J.; Tesarova, E.; Gas, B. *Electrophoresis* **2010**, *31*, 1435–1441.

(71) Phatthiyaphaibun, K.; Som-Aum, W.; Srisa-Ard, M.; Threeprom, J. *J. Anal. Chem.* **2010**, *65*, 803–808.

(72) Perez-Fernandez, V.; Garcia, M.; Marina, M. *J. Chromatogr., A* **2011**, *1218*, 4877–4885.

(73) Liu, P.; He, W.; Qin, X.; Sun, X.; Chen, H.; Zhang, S. *Chirality* **2010**, *22*, 914–921.

(74) Martinez-Giron, A.; Crego, A.; Gonzalez, M.; Marina, M. *J. Chromatogr., A* **2010**, *1217*, 1157–1165.

(75) Wan Ibrahim, W.; Hermawan, D.; Sanagi, M.; Aboul-Enein, H. *Chromatographia* **2010**, *71*, 305–309.

(76) Chen, Y.; Zhang, J.; Zhang, L.; Chen, G. *Electrophoresis* **2010**, *31*, 1493–1497.

(77) Hermawan, D.; Ibrahim, W.; Sanagi, M.; Aboul-Enein, H. *J. Pharm. Biomed. Anal.* **2010**, *53*, 1244–1249.

(78) Perez-Fernandez, V.; Garcia, M.; Marina, M. *Electrophoresis* **2010**, *31*, 1533–1539.

(79) Cheng, H.; He, B.; Zhang, Q.; Tu, Y. *Anal. Sci.* **2010**, *26*, 1087–1092.

(80) Wang, B.; He, J.; Shamsi, S. *J. Chromatogr. Sci.* **2010**, *48*, 572–583.

(81) He, J.; Shamsi, S. *Electrophoresis* **2011**, *32*, 1164–1175.

(82) Chen, B.; Du, Y. *J. Chromatogr., A* **2010**, *1217*, 1806–1812.

(83) Hu, S.; Chen, Y.; Zhu, H.; Shi, H.; Yan, N.; Chen, X. *J. Chromatogr., A* **2010**, *1217*, 5529–5535.

(84) Yu, L.; Ye, H.; Zheng, L.; Chen, L.; Chu, K.; Liu, X.; Xu, X.; Chen, G. *Electrophoresis* **2011**, *32*, 218–222.

(85) Rizkov, D.; Mizrahi, S.; Cohen, S.; Lev, O. *Electrophoresis* **2010**, *31*, 3921–3927.

(86) Zhang, H.; Qi, L.; Qiao, J.; Mao, L. *Anal. Chim. Acta* **2011**, *691*, 103–109.

(87) Kodama, S.; Taga, A.; Yamamoto, A.; Ito, Y.; Honda, Y.; Suzuki, K.; Yamashita, T.; Kemmei, T.; Aizawa, S. *Electrophoresis* **2010**, *31*, 3586–3591.

(88) Chen, B.; Du, Y.; Wang, H. *Electrophoresis* **2010**, *31*, 371–377.

(89) Yu, T.; Du, Y.; Chen, B. *Electrophoresis* **2011**, *32*, 1898–1905.

(90) Tong, M.; Payagala, T.; Perera, S.; MacDonnell, F.; Armstrong, D. *J. Chromatogr., A* **2010**, *1217*, 1139–1148.

(91) Kwon, C.; Jung, S. *Carbohydr. Res.* **2011**, *346*, 133–139.

(92) Nojavan, S.; Fakhari, A. *Electrophoresis* **2011**, *32*, 764–771.

(93) Yang, F.; Du, Y.; Chen, B.; Fan, Q.; Xu, G. *Chromatographia* **2010**, *72*, 489–493.

(94) Ma, Z.; Zhang, L.; Lin, L.; Ji, P.; Guo, X. *Biomed. Chromatogr.* **2010**, *24*, 1332–1337.

(95) Dong, Y.; McGown, L. *Electrophoresis* **2011**, *32*, 1735–1741.

(96) Kitagawa, F.; Kubota, K.; Sueyoshi, K.; Otsuka, K. *J. Pharm. Biomed. Anal.* **2010**, *53*, 1272–1277.

(97) Zaidi, S.; Han, K.; Hwang, D.; Cheong, W. *Electrophoresis* **2010**, *31*, 1019–1028.

(98) Zaidi, S.; Lee, S.; Cheong, W. *J. Chromatogr., A* **2011**, *1218*, 1291–1299.

(99) Zaidi, S.; Lee, S.; Al, O.; Zeid, A.; Al Majid, A.; Cheong, W. *Chromatographia* **2011**, *73*, 517–525.

(100) Huang, B.; Chen, Y.; Wang, G.; Liu, C. *J. Chromatogr., A* **2011**, *1218*, 849–855.

(101) Liao, S.; Wang, X.; Lin, X.; Wu, X.; Xie, Z. *J. Sep. Sci.* **2010**, *33*, 2123–2130.

(102) Li, Y.; Song, C.; Zhang, L.; Zhang, W.; Fu, H. *Talanta* **2010**, *80*, 1378–1384.

(103) Yuan, R.; Wang, Y.; Ding, G. *Anal. Sci.* **2010**, *26*, 943–947.

(104) Chen, J.; Hsieh, K. *Electrophoresis* **2011**, *32*, 398–407.

(105) Puchalska, P.; Pittler, E.; Trojanowicz, M.; Guebitz, G.; Schmid, M. *Electrophoresis* **2010**, *31*, 1517–1520.

(106) Huang, K.; Zhang, X.; Armstrong, D. *J. Chromatogr., A* **2010**, *1217*, 5261–5273.

(107) Zhang, Y.; Breitbach, Z.; Wang, C.; Armstrong, D. *Analyst* **2010**, *135*, 1076–1083.

(108) Zhang, Y.; Armstrong, D. *Analyst* **2011**, *136*, 2931–2940.

(109) Xie, S.; Zhang, Z.; Wang, Z.; Yuan, L. *J. Am. Chem. Soc.* **2011**, *133*, 11892–11895.

(110) Drake, S.; Morrison, C.; Smith, F. *Chirality* **2011**, *23*, 593–601.

(111) Saito, K.; Hosono, K.; Kitazawa, N.; Iwasaki, Y.; Ito, R.; Nakazawa, H. *J. AOAC Int.* **2011**, *94*, 923–930.

(112) Pietrogrande, M.; Basaglia, G. *J. Chromatogr., A* **2010**, *1217*, 1126–1133.

(113) Araujo, J.; Rodriques, R.; Eusebio, M.; Mota, J. *J. Chromatogr., A* **2010**, *1217*, 5407–5419.

(114) Ribeiro, A.; Gomes, P.; Pais, L.; Rodriques, A. *Chirality* **2011**, *23*, 602–611.

(115) Acetti, D.; Langel, C.; Brenna, E.; Fuganti, C.; Mazzotti, M. *J. Chromatogr., A* **2010**, *1217*, 2840–2846.

(116) Wei, Y.; Du, S.; Ito, Y. *J. Chromatogr., B* **2010**, *878*, 2937–2941.

(117) Tong, S.; Yan, J.; Guan, Y.; Lu, Y. *J. Chromatogr., A* **2011**, *1218*, 5602–5608.

(118) Tong, S.; Guan, Y.; Yan, J.; Zheng, B.; Zhao, L. *J. Chromatogr., A* **2011**, *1218*, 5434–5440.

(119) Tong, S.; Yan, J.; Guan, Y.; Fu, Y.; Ito, Y. *J. Chromatogr., A* **2010**, *1217*, 3044–3052.