

What's New in Chromatographic Enantioseparations

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Abstract: Progress in different areas of enantioselective chromatography and its applications in last years (2002-2003) is reviewed. Special attention is devoted to chromatographic enantioseparations of different drugs and natural compounds.

1. INTRODUCTION

Chromatographic enantioseparations are under constant development in methodology and applications in various fields. The most important of these applications are within pharmaceutical, environmental and clinical analysis, where the optical purity of drugs, toxins, and pollutants, as well as their enantioselective fate in the living organism may have very important implications in human health and/or effective therapy. The recent progress covered in this review concerns the last two years (2002-2003). Earlier information on that subject may be found in original papers cited in numerous reviews and monographs of either general or more specialized character of which some selected representative examples are presented in Table 1 [1-19].

Excluded from this review are electromigration techniques but an interested reader can easily find the newest pertinent information in the special issue [20] with reviews and articles devoted entirely to the subject.

2. INDIRECT MODE ENANTIOSEPARATIONS

The most important in indirect mode chromatographic enantioseparations are chiral derivatizing reagents converting racemic mixtures in mixtures of diastereomeric derivatives differing in physicochemical properties and separated on that principle. Therefore, there is a constant search for new and better derivatizing reagents and last years brought also promising results in that field. The family of chiral thiol reagents has been enriched in *N*-(*tert*-butylthiocarbamoyl)-L-cysteine ethyl ester (BTCC) [21] and this reagent was found useful for indirect HPLC enantioseparations of amino acids, amino alcohols and catecholamines and was applied for the aspartate racemase assay.

A series of new chiral derivatizing reagents was obtained by substituting one chlorine atom in cyanuric chloride by alkoxy and aryloxy substituents and other one by amino acids derived moieties (L-alanine amide, L-phenylalanine amide, L-proline *tert*-butyl ester or Boc-L-lysine *tert*-butyl

ester) or substituting both these atoms consecutively by L-valine amide and L-phenylalanine amide [22]. The reagents were evaluated for indirect HPLC separations of selected aminoacids. For the same purpose served new chiral derivatizing reagent of isothiocyanate family, namely (1*S*,2*R*)-1-acetoxy-1-phenyl-2-propyl isothiocyanate and its performance was compared with the similar (1*S*,2*S*)-1,3-diacetoxy-1-(4-nitrophenyl)-2-propyl isothiocyanate [23]. Despite the close similarity of these reagents their resolving properties were sometimes significantly different.

Several papers report recent new applications of already known derivatizing reagents. Thus (+)-1-(9-fluorenyl)ethyl chloroformate [(+)-FLEC] was used to derivatize DL-homoalanine-4-yl(methyl)phosphinate (glufosinate) herbicide for its enantioselective quantitative determination in serum and urine [24], as well as for indirect determination of D-carnitine as an impurity in L-carnitine [25], whereas its optical antipode [(-)-FLEC] served for derivatization of primary and secondary amphetamines [26]. Amphetamine related compounds were both derivatized with (S)-(-)-*N*-(fluoroacetyl)-propyl chloride [27] and with *o*-phthalaldehyde (OPA) in combination with *N*-acetyl-L-cysteine (NAC) [28]. In the first case, indirect determination of enantiomers was done by capillary gas chromatography with mass spectrophotometry and flame-ionization detection and the method was applied for determination of (S)-(+)-methamphetamine in human forensic samples and enantioselective analysis of amphetamine and fenfluramine in rat liver microsomes. In the second, the diastereomers formed were separated by RP-HPLC and served for determination of amphetamine, norephedrine and 4-methylenedioxy-amphetamine in plasma and urine. Combination of OPA with *N*-isobutyl-L-(or D)-cysteine was used for derivatization of amino acids enantiomers and their HPLC determination in various plant materials [29]. Conversely, *N*-protected-L-amino acids were used for derivatization of enantiomers of [1,1']binaphthalenyl-2,2'-diol and its 6,6'-dibromo derivative prior to their TLC separation [30]. Racemic alcohols were derivatized with (S)-(+)-2-methoxy-2-(1-naphthyl)propionic acid and the resulting diastereomeric esters were well resolved by HPLC and served for determination of absolute configurations by the ¹H NMR anisotropy method [31].

2,3,4,6-Tetra-O- β -glucopyranosyl isothiocyanate (GITC) was used for derivatization of α -adrenergic blocker -

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Table 1. Titles of Selected Reviews and Monographs on Chromatographic Enantioseparations

No.	Title	Ref.
1.	Recent progress of chiral stationary phases for HPLC	[1]
2.	Recent progress in chromatographic enantioseparations	[2]
3.	The evolution of chiral stationary phases for liquid chromatography	[3]
4.	Chiral separations by chromatography	[4]
5.	SFC of drug enantiomers	[5]
6.	Chiral separations	[6]
7.	Separation of enantiomers: needs, challenges, perspectives	[7]
8.	Unusual effects of separation conditions on chiral separation	[8]
9.	Enantioseparations in super- and subcritical fluid chromatography	[9]
10.	Enantioseparations in counter-current chromatography and centrifugal partition chromatography	[10]
11.	Preparative enantioseparation by simulated moving bed chromatography	[11]
12.	Use of atmospheric pressure ionization mass spectrometry in enantioselective liquid chromatography	[12]
13.	Chiral separation by chromatographic and electromigration techniques. A review	[13]
14.	Recent applications of stereoselective chromatography	[14]
15.	Practice and theory of enantioselective complexation gas chromatography	[15]
16.	The role of cyclodextrins in chiral selective chromatography	[16]
17.	Chiral separations using gas chromatography	[17]
18.	Stereoselective separations: Recent advances in capillary electrophoresis and high-performance liquid chromatography	[18]
19.	Enantioselective ligand exchange in modern separation techniques	[19]

propranolol enantiomers in their assay by RP-HPLC in transgenic Chinese hamster CHL cell lines and evaluation of activity of some subtypes of cytochrome P450 [32].

Different chiral acyl moieties were introduced to the nitrogen atom of 1-methyl,1,2,3,4-tetrahydro- β -carboline and these (1S) and (1R) diastereomers were separated by normal- and reversed-phase HPLC. The observed diastereomer selectivities were rationalized in terms of calculated conformations of the compounds [33].

3. DIRECT MODE ENANTIOSEPARATIONS

3.1. New Chiral Stationary Phases (CSPs)

Although a lot of CSPs of different kind have been designed and many of them are on the market there is a constant search for new representatives of this family. A brief account on updates in the technology and application of CSPs was published recently [34]. Experimental research deal both with new modifications of already known CSPs (mainly polysaccharides and cyclodextrin derivatives) and entirely new specimens with synthetic or natural chiral selectors. Within this first group novel CSPs were obtained by immobilization of chiral selector (heptakis(6-azido-6-deoxy-2,3-di-O-phenylcarbamoylated)- β -cyclodextrin [35] or methylated β -cyclodextrin [36] onto silica via multiple urea-linkages. The first CSP was found useful for HPLC

enantioseparations of some aromatic alcohols, amines and β -blocker drugs (for example, nadolol [37]), also enantiomers of several fragrance and flavor compounds were successfully separated. β -Cyclodextrin hydroxyl groups were modified with phenyl carbamate residues and this selector was bonded to silica gel by a "one pot" process simpler and faster than earlier procedures [38]. The chiral recognition of the obtained CSP was tested for many drugs and herbicides and compared with similar CSPs demonstrating sometimes better separating properties. Several norborn-2-ene β -cyclodextrin derivatives yielded CSPs by ring-opening metathesis graft polymerization that were used for enantioseparations of planar chiral ferrocene derivatives [39].

Mono(6^A-N-allylamino-6^A deoxy)perphenylcarbamoylated β -cyclodextrin chiral selector was also synthesized and immobilized on silica gel yielding another CSP for HPLC enantioseparations of different drugs [40]. Bai *et al.* [41] reported synthesis of three β -acid type CSPs based on *o*- *m*- and *p*-chloro substituted phenyl carbamates of β -cyclodextrin but it was found that they have reduced enantioseparation capacity under reversed-phase conditions, whereas under normal-phase conditions the first CSP had worse chiral recognition properties than the others in relation to five chiral test compounds. An interesting example of two crown ether-capped β -cyclodextrin bonded CSPs, i.e. 8-aminoquinoline-2-ylmethyl- and 8-aminoquinoline-7-ylmethyl-diaza-18-crown-6-capped [3-(*O*- β -cyclodextrin)-2-hydroxypropyl silica particles was recently described [42]. These

phases were used for enantioselective ultrahigh pressure capillary liquid chromatography and demonstrated high column efficiency and good enantioseparations for the tested racemates.

Cyclodextrin derivatives are often used in enantioselective gas chromatography and new representatives of modified β -cyclodextrin were obtained by substitution of 3-OH group of 2,6-di-O-pentyl- β -cyclodextrin with different acyl moieties (butyryl, valeryl, heptanoyl and octanoyl) [43]. The resulted CSPs were used for enantioseparations of different pyrethroid acid methyl esters (intermediates in preparation of pyrethroid insecticides) and other chiral compounds. Other CSPs were obtained by substitution of 2,6-OH groups with benzyl and 3-OH group with acyl groups (valeryl, heptanoyl and octanoyl). The enantioselectivity of these CSPs tested on various racemates sometimes varied but they found application in the determination of enantiomeric excess in the asymmetric synthesis of 1-(2,4-dichlorophenyl)ethanol and trans-2,3-epoxyhexanol [44]. Similar substitution of 3-OH groups but different of 2,6-OH groups (by allyl moieties) resulted in new CSPs tested for their properties and among those enantioselectivities as capillary GC CSPs [45]. Ruderisch *et al.* described mixed CSP being a combination of already known Chirasil-Calixval and Chirasil-Dex CSPs. The combined chiral selectors (resorcinarene derivative with pendant L-valine diamide groups and permethylated β -cyclodextrin) bonded to poly(hydroxymethyl)dimethylsiloxane showed additive enantioselective effects towards various racemates. [46]. A new modification of Chirasil-Dex with a C11 spacer and its applications were also described [47]. Chen and Shi [48] synthesized 2,3-di-O-pentyl- β -cyclodextrin derivatives with valeryl, heptanoyl and octanoyl groups in the 6-position and tested them on 15 racemates as CSPs for capillary gas chromatography. The best enantioselectivity was found for CSP with valeryl substituent.

New CSPs based on cellulose derivatives were also obtained and their enantioselectivity and applications studied. Thus, cellulose trisphenylcarbamate was bonded to both 3-aminopropyl and underivatized silica gel through 6-hydroxy group and a spacer from 4,4'-diphenylmethane diisocyanate reagent. It was found that these bonded-type phases showed higher column efficiency but a lower chiral recognition ability when compared with their coated-type counterparts under HPLC conditions [49]. Another type of spacer reagent used was 3-(triethoxysilyl)propyl isocyanate and the CSPs were obtained by non-regioselective and regioselective procedures. These last resulted generally in slightly better resolution power but were more time-consuming. Pore size of silica gel also effected the enantioselectivity [50]. Francotte and Huynh prepared new CSPs from 3,4- and 3,5-dichlorophenylcarbamate, and 3-trifluoromethyl-4-chlorophenylcarbamate derivatives of cellulose immobilized on silica gel by UV irradiation.[51]. Their enantioselective properties were tested against 15 racemates using different mobile phases and the results discussed in terms of modulation of chiral recognition of polysaccharide based CSPs.

Cyclopentyl and (\pm)-exo-2-norbornylcarbamates of cellulose and amylose CSPs were prepared and tested for chiral recognition of 13 different racemates [52]. Cellulose 3,5-dimethylphenylcarbamate derivatives with a vinyl

moiety (4-vinylphenylcarbamate or 2-methacryloyloxyethylcarbamate) at the 6-position were immobilized on silica gel through the radical copolymerization with styrene [53]. The resulting CSPs proved to be stable with the eluent containing 10% chloroform which was advantageous for HPLC enantioseparation of some racemates.

Mixed 4-(10-undecenyloxybenzoate/4-methyl (and 4-methoxy) benzoates of cellulose were immobilized on silica gel and these CSPs were compared with CSPs having 10-undecenyl group [54]. It was found that the introduction of additional aromatic moiety in the fixing substituent resulted in an improvement of chiral recognition ability.

Several chitin carbamate derivatives were synthesized and immobilized on silica gel yielding CSPs for HPLC resolution [55]. The best chiral recognition was found for 3,5-dimethylphenyl, 4-chlorophenyl and 4-trifluoromethylphenylcarbamates and other properties of these phases were also investigated. Also synthetic polysaccharides, 2,3,4-tris-O-(3,5-dimethylphenylcarbamoyl)- and 2,3,4-tris-O-(3,5-dichlorophenylcarbamoyl)-(1-6)-D-glucopyranan and their (1-6)-D-mannopyranan counterparts were synthesized and evaluated as CSPs [56].

Amino acids and their derivatives for a long time have been chiral selectors for different CSPs and this trend is also continued nowadays. It may be exemplified by new CSPs prepared by bonding to silica gel such compounds like (S)-phenylglycine and (R)-4-methoxyphenylglycine [57], (S)-N,N-carboxymethyl undecyl leucinol monosodium salt [58], (R)-N,N-carboxymethyl undecyl phenylglycinol monosodium salt [59], N-(3,5-dimethylbenzoyl) derivatives of (R)-alaninol, (S)-leucinol, (S)-tert-leucinol and (1S,2R)-ephedrine, as well as O-(3,5-dinitrobenzoyl) derivative of (R)-phenylglycinol [60]. Interesting biselectors CSPs were obtained from (R)- or (S)-1-(1-naphthyl)ethylamine, (S)-N-3,5-dinitrobenzoylphenylglycine, (S)-N-3,5-dinitrobenzoyl-leucine and (R)- or (S)-N-1-naphthoylphenylglycine connected to s-triazine [61,62]. N-tert-butoxycarbonyl derivatives of some L-amino acids (alanine, leucine and phenylglycine) served as starting material for preparation of CSPs based on their 3,5-dimethylanilides of N-(4-alkylamino-3,5-dinitro)benzoyl derivatives [63]. Mono- and polymeric CSPs were synthesized from chiral monomers shown in (Fig. 1) (**1** and **2**) [64], whereas acryloyl-L-valine N-methylamide and N,N-diamide yielded polymers bound on silica gel supports [65]. A new diamide-type CSP was prepared by bonding the N-stearoyl-L-leucine with the aminopropyl silica gel [66]. This phase was used with success for enantioresolution of amino acids and some of their derivatives in reversed phase mode and normal phase mode, respectively. Cu(II) complexes with L-amino acylamides proved useful as CSPs for micro liquid chromatography and electrochromatography but also for chiral selectors in capillary electrophoresis for enantioseparation of dansyl derivatives of amino acids [67]. Urea-formaldehyde resin microspheres modified with L-proline were new CSP for liquid chromatography acting on ligand exchange principle [68].

Novel CSPs with selectors of crown-ether type based on (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid [69] and compounds **3** and **4** (Fig. 1) [70] were recently described. Among synthetic selectors used for preparation of new CSPs were: N-n-decyl-L-spinacine (**5**, Fig. 1) [71], 4-chloro-3,5-

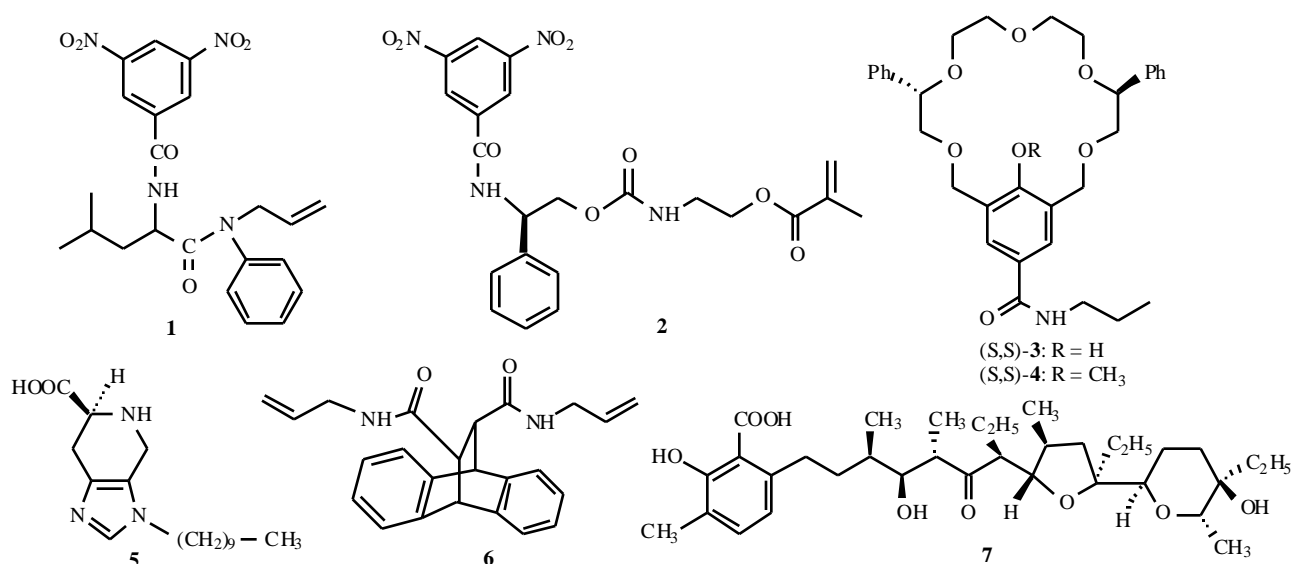


Fig. (1). Selected chiral selectors of new CSPs.

dinitrobenzoic acid amides of α -aminoalcohols and α -arylethylamines ((1S,2R)-cis-1-amino-2-indanol, (1R,2S)-norephedrine, L-alaninol, L-phenylglycinol, (R)-1-phenylethyl amine, (R)-1-(1-naphthyl)ethyl amine and (R)-cyclohexylethyl amine) [72] and bis-allyl amide of dicarboxylic acid obtained by a Diels-Alder reaction between fumaric acid and anthracene **6**, Fig. 1 [73]. Chiral selectors used for the same purpose but originated from natural compounds comprise an enzyme - penicillin G acylase [74], polyether antibiotic - lasalocid **7**, Fig. 1 [75], 9-(tert-butylcarbamoyl)-6-neopentoxycinchonidine [76], cholesterol [77] and antibiotic of teicoplanin family - MDL 63,246 [78]. All the new CSPs were characterized and their enantioselectivity tested under different conditions and discussed for various racemates.

The efforts to prepare highly specific selectors for CSPs able to separate enantiomers of only narrow class of compounds or single racemic species led to such materials like stereoselective monoclonal antibodies to D- and L- amino acids, raised against protein conjugates of p-amino-D- and L-phenylalanine [79] or a DNA aptamer binding stereospecifically the D-enantiomer of an oligopeptide - arginine-vasopressin [80].

The same idea of high stereospecificity is bound with preparation of molecularly imprinted polymers (MIPs) and their use, among other purposes, as CSPs in liquid chromatography. Various compounds were used as template molecules, such as (-)-ephedrine [81], (+)-chlorpheniramine [82], 2-L-, 3-L- and 4-L-phenylalanyl-amino-pyridines [83], N-benzyloxycarbonyl-L-glutamic acid [84], N-(carbobenzyl)-L-tryptophan, Fmoc-L-tryptophan, cinchonine, cinchonidine, quinidine and quinine, [85] and (S)-nilvadipine [86].

The role of different functional monomers and cross-linkers, polymerization and chromatographic conditions and their effect on LC enantioselectivity performance were extensively studied, as exemplified by the study of chiral recognition of MIP with 4-L-phenylalanyl-amino-pyridine [87]. Finally, an interesting combinatorial approach used for preparation of new highly enantioselective CSPs for HPLC

is worth mentioning [88]. Chiral selectors were searched in the library of phenyl amides of 2-oxo-azetidinoacetic acid derivatives.

This rich choice of novel CSPs for HPLC far exceeds that for GC, represented by discussed above α -cyclodextrin derivatives and copolymeric (1R-trans)-N,N'-1,2-cyclohexylenebisbenzamide oligodimethylsiloxane tested on over 30 different racemic analytes [89].

3.2. Mechanisms of Enantioselectivity

There is a continuous research on mechanisms of enantioselectivity of chiral selectors and enantioselectivity on both new and old CSPs used in HPLC. Different techniques are used for that purpose, such as NMR, circular dichroism, molecular modeling, quantitative structure-enantioselective retention relationships, determination of thermodynamic parameters, etc. Only a short account on these studies performed recently may be given here, based on the types of CSPs investigated.

The data of enantiomeric resolution of (\pm)-threo-methylphenidate on cellulose tribenzoate CSP (Chiralcel OB) and molecular modeling led to conclusion that the separation of these enantiomers may be governed by the π - π stacking interactions, but hydrogen bonding and dipole-induced dipole interactions are also essential [90]. The binary isotherms were measured for HPLC enantioselectivity of the Troger's base enantiomers and their behavior on Chiralpak AD CSP studied [91]. The binary adsorption isotherms of enantiomers of 1-phenyl-1-propanol were measured on a microbore column with Chiralcel OB phase and the bi-Langmuir model proved to be the best for optimization of preparative enantioselectivity [92]. General rate model, generalized Maxwell-Stefan equation and Tóth isotherm model were also applied for this enantioselectivity [93] and numerical determination of the competitive isotherm was also described [94]. Similar approach was used for investigations on enantioselectivity of 1-indanol using inverse method for determination of adsorption isotherms [95] and different size columns with Chiralcel OB [96,97].

Enantiomeric resolution on other polysaccharide CSPs [cellulose triacetate - Chiralcel CA-I, cellulose tris(4-chlorophenylcarbamate) - Chiralcel OF and cellulose 4-methylphenylcarbamate - Chiralcel OG] of 7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene and its 6-fluoro- and bromo-derivatives was used for preliminary discussions on structure-enantioresolution relationships [98].

Cass *et al.* studied the enantioseparation of different drugs (omeprazole, lansoprazole, pantoprazole and metyrapol) in different elution modes on columns with CSPs of cellulose and amylose tris(3,5-dimethylphenylcarbamate), amylose tris(3,5-dimethoxyphenylcarbamate) and tris[(S)-1-phenylethylcarbamate] found that the differences in enantioselectivity and enantioresolution depend solely on the mobile phase effects [99]. On the other hand, studies on effect of alcohol mobile-phase modifiers on the enantioselectivity of amylose tris(3,5-dimethylphenylcarbamate) CSP (Chiralpak AD) revealed structural changes of that phase caused by those modifiers of different bulkiness and by changes in concentration of the modifier [100]. Wang *et al.* reported that separation of enantiomers of dihydropyrimidinone acid and methyl ester on Chiralpak AD column dependence on temperature suggests thermally induced irreversible conformational change of this CSP [101,102]. This change depended on the polar component of the mobile phase occurring for ethanol modifier but not for 2-propanol.

Separations of enantiomers of norgestrel with α -, β - and γ -cyclodextrins used as mobile phase additives were studied by HPLC, capillary electrophoresis and NMR methods. The association constants calculated from the chemical shift data of single enantiomers proved useful for optimization of chromatographic and CE enantioseparations [103]. On the base of studies on HPLC resolution of enantiomers of 2-alkoxy-substituted esters of phenylcarbamic acid on α - and β -cyclodextrins Hrobonowa *et al.* concluded that non-polar interactions between CSP and these enantiomers had the greatest effect on enantioresolution and the length of the alkoxy substituent and its position with respect to the asymmetric carbon atom have the dominant effect on enantioseparation [104,105]. An excellent example of studies using different methods on enantiomeric recognition of β -cyclodextrin was given in the paper of Zhou *et al.* [106]. It was demonstrated that NMR was superior for structural elucidation of complexes formed, ESI-MS gave evidence for their stoichiometry, whereas CE was superior in terms of direct enantioseparation. Chiral recognition of the same cyclodextrin with N-acetyl- and N-carbobenzoxy-dipeptides possessing 2 aromatic rings was studied by microcalorimetric and NMR techniques [107].

Chiral discrimination in HPLC of both the dansyl leucine cyclohexylammonium ion pair enantiomers and free dansyl leucine anion enantiomers by β -cyclodextrin CSP had mainly enthalpic driving forces and the cavity of the selector was the primary site of chiral recognition [108]. Molecular dynamics and NMR spectroscopy were used for studies of Lipodex E CSP [octakis(3-O-butanoyl-2,6-di-O-pentyl)- β -cyclodextrin] used in enantioselective gas chromatography [109]. It was found that the selector molecule shows a larger equilibrium deformation of the macrocycle from the idealized geometry than native β -cyclodextrin and one of the pentyl chains is self-included in the cavity. A very high

separation factor was obtained for enantiomers of decomposition product of sevoflurane (an inhalation anesthetic) on this CSP and thermodynamic parameters were determined to explain this phenomenon [110]. Interestingly, the enantioselectivity was markedly reduced or even zeroed for α - and γ -cyclodextrin CSP analogs, respectively.

Chiral recognition ability of β -cyclodextrin under gas-liquid chromatographic conditions was studied for enantioseparations of several chiral monoterpenoids [111]. The results indicated that only the second step of complexation displayed marked enantioselectivity.

Reversible and covalent binding of drugs to human serum albumin (HSA) was thoroughly discussed by Bertucci and Domenici [112], among others, also in terms of usage of biochromatography for characterization of binding sites and enantioselectivity of this CSP. Separations of enantiomers of several bioactive compounds (aryl propionic acids [113], valproate [114]) were investigated for the same purpose. The mechanism of enantioseparation of CSPs obtained by binding of HSA to silica by means of polymers was also studied [115].

The adsorption properties and their modifications of β -acid glycoprotein CSP (CHIRAL-AGP) were studied in relation to the mechanism of chiral recognition [116,117], whereas this CSP was used for experimental verification of theory for binary perturbation peaks in chiral liquid chromatography [118]. Chiral recognition of chicken β -acid glycoprotein was described to the protein domain of this ovoglycoprotein from chicken egg whites [119]. Quantitative structure-enantioselective retention relationships were used for investigations of chiral retention mechanism of immobilized riboflavin binding protein CSP [120]. Different racemates of β -receptor agonists and antagonists were used as test compounds and their hydrophobic interactions with the riboflavin binding site were found mainly responsible for retention, whereas polar interactions were of secondary importance. Thermodynamic parameters indicated that both retention and enantioselectivity of this CSP were enthalpically driven.

Studies of some aspects of enantioselective mechanisms of Pirkle-type CSPs comprise, among others, conformational effects on the recognition of enantiomers of some 1,2,3,4-tetrahydrophenanthrene derivatives by a Naproxen-derived CSP [121] and retention of 1'-bis(2-naphthol) atropisomers on CHIRIS AD1 and AD2 columns [122].

Enantioseparations of aryl- and heterarylcarbinols on (S,S)-3,5-dinitrobenzoylated 1,2-diphenylethane-1,2-diamine CSP (ULMO) were modeled by 3-D-QSAR methods (CoMFA and CoMSIA) [123]. NMR was used to study enantioseparation of N-acylnaphthylethylamines by (R)-phenylglycinol N-3,5-dinitrobenzoyl-O-triethoxysilylpropylcarbamate as a chiral selector [124]. Selectivities and retentions of two Pirkle CSPs with (R)-3,5-dinitrobenzoylphenylglycine and (S)-3,5-dinitrobenzoylleucine chiral selectors were compared by correlation method [125] and the determination of absolute configuration of chiral amines was based on chiral recognition mechanism of the Whelk-O 1 CSP [126].

Several papers were devoted to mechanisms of chiral recognition on macrocyclic glycopeptide antibiotic chiral selectors. Thus, studies of chiral discrimination of four phenoxypropionic acid herbicides on teicoplanin CSP in

RP-HPLC revealed temperature dependent change in conformation of the chiral selector and increasing enantioselectivity with an increase of methanol content in the mobile phase, attributed to restriction of the solute association in the CSP [127]. Further refinement of this results were done using a bi-Langmuir model [128]. Similar investigations were done for enantioseparation of dansylated amino acids in the presence of saccharose and perchlorate anion in the mobile phase [129]. The thermodynamic data indicated that the sugar affected only the hydrophobic part of the interaction CSP-dansyl amino acid. An increase of the separation factor parallel to increased perchlorate salt concentration was enthalpically controlled owing to stereoselective bonding interactions. The effect of sodium perchlorate was also investigated in the enantioseparation of tryptophan [130].

Enantioseparation of alkoxy-substituted derivatives of phenylcarbamic acid was compared on two teicoplanin-derived CSPs - with (Chirobiotic T) and without carbohydrate moieties (Chirobiotic TAG) [131]. Better separations were found for teicoplanin aglycone CSP and this method was used to determine these compounds in rabbit blood serum [132].

The mechanism of enantioselectivity of vancomycin CSP was studied with the use of racemic dansyl derivatives of amino acids (Val, Ser, Leu and Phe) and N-acetyl-D-alanine (competing agent) in the mobile phase [133]. It was demonstrated that the solutes enantioselectively bind to the aglycone pocket of the selector but also additional enantioselective sites of vancomycin are involved in chiral discrimination. Chiral recognition of vancomycin used as a chiral mobile phase additive separating enantiomers of dansylated valine was also investigated and the dimerization of chiral selector was indicated as an important factor of this process [134]. This dimerization was also studied using enantioseparations of dansyl derivatives of serine and valine on amino Nucleosil stationary phase [135]. Heterodimerization between ristocetin CSP chiral selector and vancomycin used as chiral mobile phase additive was also postulated for enantioseparations of racemic tryptophan and its dansyl derivative [136]. The effects of temperature and solute molecular size on the retention and enantioselectivity of dansyl amino acids on a vancomycin-based CSP were also studied [137]. The interactions of ristocetin A CSP with some chiral compounds (tryptophan and its derivatives, 1-[5-chloro-2-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline and -phenyl- -butyrolactone) were elucidated by investigations of effect of temperature on enantioseparations and measurement of thermodynamic parameters for different mobile phase compositions and different chromatographic modes (reversed phase, polar-organic and normal phase) [138]. Hyun *et al.* [139] found that tethering groups of (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid CSP play an important, although still not fully understood, their role on the HPLC enantioseparation of α -amino acids.

3.3. Preparative Enantioseparations

There is no doubt that preparative enantioseparation of drugs and drug candidates is one of the most important problems of stereoselective chromatography, both from theoretical and practical point of view. A minireview on that

subject was published recently [140] and many experimental papers which appeared in last years reported new results.

A quick method for determination of the optimal operating conditions of a four-column simulated moving bed (SMB) unit for a separation of enantiomers of 1,1'-bi-2-naphthol enantiomers on D-phenylglycine CSP was proposed by Lai and Loh [141] and the enantioseparation of the same compound on the same CSP was also studied on the eight-column unit [142]. Jupke *et al.* [143] discussed the strategy for the optimal choice of all process parameters for SMB and batch processes. The productivity of enantioselective SMB process in terms of adsorption isotherms for separation of enantiomers of α -ionone [144] and mandelic acid [145] was also investigated. The SMB process combined with supercritical fluid chromatography (SFC) gave good results for separation of 1,1'-bi-2-naphthol enantiomers on Kromasil CHI-DMB and Chiralcel OJ phases [146]. Gas phase SMB process was applied for the preparative separation of enantiomers of the inhalation anesthetic enflurane on octakis(3-O-butanoyl-2,6-di-O-n-pentyl)- α -cyclodextrin CSP [147]. The intelligent chiral resolution system was proposed for method development for preparative enantioselective separations [148] taking polar solvents as the first choice for eluent systems for polysaccharide CSPs. Investigators from industrial laboratories described optimization of SMB and Varicol processes, both are consisting of a number of columns connected in series, and found the superiority of this second, especially when few columns were used [149]. This approach was exemplified by the separation of enantiomers of SB 553261 (from GlaxoSmithKline) and those of propranolol [150]. The same conclusions were also reported by other investigators [151]. On the other hand, changing of internal and external liquid flow-rates during the switching period in the SMB process makes its performance comparable with that of the Varicol process [152]. An interesting example of enantioseparation of more than thousand kilograms of pharmaceutical racemate by batch and SMB chromatography was reported [153]. Preparative and analytical HPLC enantioseparations of new acetylcholinesterase inhibitors on Chiralcel OD column [154] and phosphinic acid analogs of dipeptides on cinchona alkaloid derived CSPs [155] were described, whereas similar enantioseparations of six different drugs (atropine, bendroflumethiazide and four β -blockers) on CSPs based on mono-6A-azido-6-A-deoxy-perphenylcarbamoylated α -cyclodextrin immobilized on silica gel and ten various chiral drugs were reported by Ng *et al.* [156] and Thunberg *et al.*, [157], respectively. Preparative Chiralcel OD column was used for resolution of enantiomers of muscle relaxant - chlormezanone [158], whereas trans-stilbene oxide was enantio-separated on cellulose tris(phenylcarbamate) CSP [159].

Semipreparative HPLC enantioseparations of gossypol on cellulose tris(3,5-dimethylphenylcarbamate) [160], dimethyl α -hydroxyfarnesylphosphonate (a precursor of a farnesyl protein transferase inhibitor) on Chiralcel OD column [161] and albendazole sulfoxide using supercritical chromatography on Chiralpak AC column [162] were also presented. Preparative SMB enantioseparations of precursors of gantofibrin (antithrombotic drug) [163] and combined semipreparative HPLC enantioseparation of a new anti HIV-1 agent and a base induced racemization of its less active

(R)-enantiomer may be another good examples of pharmaceutical applications [164].

4. ENANTIOSEPARATIONS OF CHIRAL COMPOUNDS

4.1. Amino Acids

Chiral amino acids are one of the most investigated group of compounds due to their role as components of peptides, starting materials for synthesis of biologically active compounds, constituents of foods and living organisms, etc. Enantioselective chromatography of these compounds was a very active research field in the past and recent years brought further developments. Both indirect and direct methods are used for separation of enantiomers of amino acids. Among these first, reaction with a new derivatizing reagent - (S)-N-(4-nitrophenoxycarbonyl)phenylalanine methoxyethyl ester, was used for RP-HPLC enantioseparation of unnatural secondary amino acids, where the amino acid moiety of the compounds was a part of the ring system [165, 166], α -alkyl substituted analogs of tyrosine, phenylalanine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid and tryptophan [167], as well as spin labelled α -amino acids [168]. These compounds were also derivatized with GITC reagent and directly enantioseparated on cellulose-derived CSP (Chiralcel OD-RH). Several enantiomers of glycine and alanine unusual analogs were separated after derivatization with GITC and N-(2,4-dinitro-5-fluorophenyl)-L-alaninamide (Marfey's reagent), as well as directly on the macrocyclic glycopeptide antibiotic (teicoplanin, ristocetin A) and crown ether CSPs [169]. Comparisons of results revealed that Marfey's reagent was more efficient than GITC, whereas antibiotic CSPs, and especially that with teicoplanin, were most effective in these enantioseparations. Nineteen biogenic amino acids were derivatized with N-fluorenylmethoxycarbonyl-L-alanyl N-carboxyanhydride and a majority of the resulting pairs of diastereomeric dipeptides was separated by HPLC [170].

More papers were devoted to direct enantioseparations. Separations of enantiomers of 25 α -amino acids on Chiralpak AD column were studied using different mobile phase additives (sulfonic acids and amines) and modifiers [171]. Satisfactory enantioseparations were reported for 20 amino acids, whereas enantiomers of arginine failed to separate and for 4 analytes (aspartic acid, citrulline, glutamine and histidine) only partial separation was achieved. Enantiomers of some β -methyl amino acids were separated by ligand exchange HPLC on L-4-hydroxyproline chemically bonded to silica gel and this chiral selector was more efficient than when used in capillary electrophoresis [172]. Francotte *et al.* reported preparative enantioseparation of N-carbobenzoxy-tert-leucine and N-Boc-tert-leucine benzylester in high yield and high optical purity on cellulose- (Chiralcel OD) and amylose- (Chiralpak AD) derived CSPs, respectively [173]. Enantioseparation of differently derivatized amino acids on amino- β -cyclodextrin CSP was described [174] and in the same paper enanteicoplanin of some biogenic amines on vancomycin and teicoplanin CSPs were also reported. Quinine-derived chiral anion exchange selectors were used for direct HPLC enantioseparation of apolar N-2,4-dinitrophenyl derivatives of unusual α -amino acids [175], N-acylated amino acids [176] and various

benzoyl, 3,5-dinitrobenzoyl and 3,5-dinitrobenzyloxy-carbonyl amino acid derivatives [177]. In this last case, non-aqueous capillary electrophoresis was also used for analogous enantioseparations and the results proved the relationship between enantioselectivity values obtained by both methods.

Different Pirkle-type CSPs served for resolutions of anilide derivatives of enantiomers of N-acyl- α -amino acids and special attention was paid to chiral recognition mechanism of CSP derived from N-3,5-dinitrobenzoyl)leucine N-phenyl N-alkylamide [178]. Enantio- and stereo- selectivities of chiral crown ether (Crownpak), teicoplanin and copper(II)-D-penicillamine CSPs were compared for resolutions of cycloaliphatic α -substituted β -quaternary α -amino acids [179]. Only one pair of enantiomers was separated on Crownpak CSP, whereas the separations on the other CSPs were much better. D-Penicillamine CSP (Chirex 3126) is also recommended for enantioseparation of amino acids in an application note [180].

The abovementioned ligand exchange CSP with (S)-N,N-carboxymethyl undecyl leucinol monosodium salt chiral selector was used for enantioseparation of α -amino acids [181]. The best results were obtained for enantiomers containing aromatic moiety in the side chain. Diphenylalanine enantiomers were resolved on the (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid CSP [182], whereas the same phase and teicoplanin aglycone CSP were used for separations of enantiomers of amino acids and their dansyl derivatives by enantioselective ion-exclusion chromatography [183]. Enantiomers of β -methyl diphenylalanine were preparatively separated by HPLC on mixed 10-undecenoate/cellulose 3,5-dimethylphenylcarbamate CSP [184]. Six N-trifluoroacetyl-O-methylesters of amino acids were enantioseparated by gas chromatography using single and two columns of opposite selectivity (Chirasil-L- and D-Val) coupled in series [185].

Finally, some applications of chiral chromatographic amino acid analysis may be mentioned. Thus, the Sumichiral OA4600 CSP and the automated column switching HPLC system were used for quantification of enantiomers of N-methylaspartate [186] and similar system was used for determination of D-alanine in rat tissues [187]. D-glutamic and D-aspartic acid contents were assayed indirectly after derivatization with o-phthalaldehyde and 2,3,4,6-tetra-O-acetyl-1-glucopyranoside for determination of protein of bacterial origin [188]. A HPLC enantioselective analysis was described for enantiomers of N-(trans-4-isopropylcyclohexylcarbonyl)-phenylalanine, of which D-antipode is an anti-diabetic agent (Nategline) [189]. Determination of human serum thyroxine enantiomers was accomplished using a chiral ligand exchange system with mobile phase of CH₃CN-aqueous eluent containing L-proline (0.2 mM), cupric acetate (0.1 mM) and triethylamine (0.5 mM) (35:65, v/v) [190]. Enantioselective GC analysis of amino acids in fortified wines, as their N(O)-pentafluoropropionyl amino acid 1-propyl esters was also reported recently [191].

4.2. Chiral Drugs

Besides preparative enantioseparations of drugs outlined above, analytical chromatographic enantioseparations of drugs and related compounds is by no means the most active

research field among enantioselective separation methods. Not only pure drug substances are subjected to this type of analysis but also drugs in body fluids, in pharmaceutical preparations, drug metabolites, drug substrates and/or intermediates and prospective drugs, i.e. biologically active substances of distinct therapeutic character.

There are many reviews describing various aspects of enantioselective chromatography of drugs. Those recently published are presented in Table 2.

Many experimental papers are devoted to enantioseparations of single drugs other report results of resolution of enantiomers for different groups of drugs or various compounds of pharmacological interest. Some investigations concentrate on effects of different chromatographic parameters on the resolution of enantiomers, other try to establish methods of their determination in dosage forms and in biological fluids and their use for elucidation of stereochemical fate of drugs in the body.

Thuau *et al.* studied chiral recognition of warfarin enantiomers by epichlorohydrin/ α -cyclodextrin polymer base supports [202], Karlsson *et al.* investigated the effect of temperature on the reversal in the retention order by the HPLC enantioseparation of mosapride on β -acid glycoprotein CSP [203], whereas the effect of acidity on the enantioseparation of thyroxine and tocainide by HPLC on crown ether CSP was described by Aboul-Enein *et al.* [204]. Enantiomeric resolution of methylphenidate was compared on different polysaccharide CSPs [205], whereas that of cisapride was investigated on one of them (Chiralcel) in direct (OJ) and reversed (OJ-R) version [206]. Different polysaccharide derived CSPs were also tested for more than 20 different drugs and their suitability for enantioseparation discussed [207]. HPLC separation of cromakalim (anti-hypertensive drug) enantiomers was achieved on teicoplanin and teicoplanin aglycone CSPs [208], whereas that of enantiomers of three antidepressive drugs (oxazepam, lorazepam and promethazine) and their on-column racemization were studied on vancomycin and teicoplanin CSPs [209]. Earlier, HPLC separation of promethazine enantiomers on vancomycin CSP and their stability were also studied

[210]. Several papers report comparison of different aspects of enantioseparations by HPLC and capillary electrophoresis. This concern such drugs as isoxsuprine (vasodilator) [211], cis-diltiazem hydrochloride and its desacetylated metabolite (calcium blocker) [212], fenticonazole (antifungal agent) [213] and M3 antagonist [214].

Different chiral selectors were tested for HPLC enantioseparations of drugs. These include (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid CSP (for gemifloxacin [215] and 5 drugs of secondary amine type, i.e. albuterol, atenolol, methoxyphenamine, pindolol and propranolol [216]), (3,3'-diphenyl-1,1'-binaphthyl)-20-crown-6 (for gemifloxacin and other fluoroquinolone antibacterials [217] and tocainide and its analogs [218]), heptakis(6-azido-6-deoxy)perphenyl-carbamated α -cyclodextrin (for tolperisone) [219] and (R)-1-naphthylglycine and 3,5-dinitrobenzoic acid CSP (for metoprolol and bisoprolol) [220]. Enantiomers of cetirizine (a histamine receptor antagonist) and related compounds were resolved on cellulose tris(3,5-dimethylphenyl)carbamate (Chiralcel OD-R column) [221]. Several chiral columns were tested for enantioseparations of antidepressant drug - reboxetine and its desethylated metabolite and their advantages and disadvantages discussed [222]. Similarly, four different approaches were investigated for enantioseparation of flurbiprofen and its two major metabolites [223]. The most appropriate was found the direct enantioseparation on Chiralpak AD and it was used for studies of influence of stereochemistry and age on disposition of flurbiprofen in man [224]. Enantioseparation of the same drug was studied on Chiralpak AD-RH column [225]. Calculation of thermodynamic parameters allowed explanations of resolution process due to distribution of the enantiomers between the cavities of the mobile [water-acetonitrile (60:40, v/v) with 0.1% acetic acid] and stationary phases. Immuno-affinity columns (anti-D-amphetamine monoclonal antibody covalently bonded to pre-activated support) were used for enantioseparations of amphetamine and/or methamphetamine [226], whereas diastereomers and enantiomers of exametazime (a technetium 99m complex of (\pm)-(RR,SS)-4,8-diaza-3,6,6,9-tetramethylundecane-2,10-dione, used in dia-

Table 2. Titles of Recently Published Reviews on Chromatographic Enantioseparations of Drugs

No.	Title	Ref.
1.	Preparative chiral chromatographic resolution of enantiomers in drug discovery	[192]
2.	Resolution of chiral drugs by liquid chromatography based upon diastereomer formation with chiral derivatization reagents	[193]
3.	Enantiomeric composition of abused amine drugs: chromatographic methods of analysis and data interpretation	[194]
4.	Strategies for the enantiomeric determination of amphetamine and related compounds by liquid chromatography	[195]
5.	Stereoselective chromatography of cardiovascular drugs: an update	[196]
6.	High-performance liquid chromatographic separation of fluoroquinolone enantiomers: a review	[197]
7.	Stereoselective determination and pharmacokinetics of dihydropyridines	[198]
8.	Pharmaceutical and biomedical applications of enantioseparations using liquid chromatographic techniques	[199]
9.	Separation of drug enantiomers by liquid chromatography and capillary electrophoresis, using immobilized proteins as chiral selectors	[200]
10.	Resolution of enantiomers of ketoprofen by HPLC: a review	[201]

gnostic nuclear medicine) were separated by ligand-exchange chromatography using chiral eluent with the complex of Cu(II) and N,N-dimethyl-L-phenylalanine [227].

Perrin *et al.* corroborated screening strategy for chiral separation of pharmaceuticals by normal-phase [228] and reversed phase [229] liquid chromatography. Similar screening procedure involving 55 enantiomeric pairs from the pharmaceutical industry (substrates, intermediates and drug substances) and polysaccharide-derived and macrocyclic glycopeptide CSPs was also recently evaluated [230]. Three polysaccharide-derived CSPs (Chiralcel OD-H, Chiralpak AD and Chiralcel OJ and their reversed-phase analogs) and 36 and 37 various drugs were used in their studies respectively. An automated screening approach based on gradient elution enantioselective HPLC resolutions on four polysaccharide columns was employed in pharmaceutical company for chiral compounds tested as prospective drugs [231]. Enantioseparation of eight drugs (cromakalim, econazole, etodolac, metoprolol, miconazole, nebivolol, teratolol and tolamolol) on cellulose tris(3,5-dichlorophenylcarbamate) CSP, with separation factors ranged from 1.24 to 3.90, was reported by Aboul-Enein and Ali [232].

Enantioseparations of different drugs on different types of CSPs and columns may be further exemplified by resolutions of enantiomers and diastereomers of ephedrine on phenyl- β -cyclodextrin-type CSP and ODS-type column [233] and enantiomers of: econazole, miconazole and sulconazole on cellulose-derived CSPs [234], mianserin, chlorthalidone and ketoprofen on resorcinarene CSPs [235], various diuretics on Pirkle-type ULMO CSP (3,5-dinitrobenzoyl derivative of 1,2-diphenylethylenediamine covalently bound to silica-packing), [236] and thiazide diuretics on cellulose-derived and teicoplanin CSPs [237], 1,4-dihydropyrimidine calcium antagonists (amlodipine, felodipine, isradipine, lercanidipine, nimodipine and nisoldipine) on vancomycin CSP (Chirobiotic V column) [238], clenbuterol on Chirex 3005 column [239], linezolid (synthetic antibiotic) on Chiralpak AD column [240], emtricitabine (an anti HIV analog nucleoside) on amylose tris[(S)-1-phenylethylcarbamate] CSP [241].

Polysaccharide columns (Chiralcel OD-H and Chiralpak AD) were used for enantioselective analysis of thioridazine and its metabolite - thioridazine 2-sulfone, and the results served for investigations on racemization and degradation of these compounds in human plasma and aqueous solutions [242].

Ultrahigh pressure liquid chromatography with β -cyclodextrin and 2-hydroxypropyl- β -cyclodextrin as mobile phase additives was used for enantioseparations of chlorthalidone, oxazepam and temazepam [243]. A distinct gain on separation time was noted since all enantioseparations were completed in 2 minutes or less.

Often supercritical fluid chromatography is used for enantioseparation of drugs, especially when supported by mass spectrometric detection, as it was demonstrated by Garzotti and Hamdan [244] and Zhao *et al.* [245]. Other examples of SFC concern enantioseparations of β -blockers of amino alcohol type, using Hypercarb column and L-(+)-tartaric acid as chiral selector [246], thiazolbenzenesulfonamide compound (a β adrenergic receptor agonist) on

Chiralpak AD column [247], twelve various drugs on Chiralpak AD and Chirobiotic V columns [248] and antifungal drug - ketoconazole and some of its precursors on Chiralpak AD and Chiralcel OD columns [249]. In this last case also HPLC enantioseparations were run for comparisons and generally the results were better when SFC was used, however, among four compounds investigated enantioseparation of one was accomplished only by HPLC.

Densitometric determination of budesonide enantiomers in pharmaceuticals is one of rather scarce examples of enantioseparation by planar chromatography [250] run on cellulose plates with 1% aqueous β -cyclodextrin solution as a mobile phase (methanol) additive. Enantiomers of different cardiovascular drugs were also resolved by this type of chromatography on synthetic polymers imprinted with (-)-(S)-timolol [251], whereas some 2-aryl propionic acids (NSAIDs) were recently enantioseparated on silica gel stationary phases impregnated with enantiomerically pure aminoacids L-(-)-serine [252] and/or L-(-)-threonine [253]. Also direct enantiomeric resolution of atenolol, metoprolol and propranolol by TLC using L-aspartic acid as a chiral impregnating agent [254] is worth mentioning.

Analysis of chiral drugs in biological material is a very important issue and a lot of research is continuously conducted in this area. Besides many earlier reviews three recently published deal directly with that subject. One discusses thoroughly the importance of stereoselective determination of drugs in clinical laboratory based on numerous examples [255], other deals with the role of chiral chromatography in therapeutic drug monitoring and in clinical and forensic toxicology [256] and the third (with 185 references) deals with the role of biological matrices during analysis of chiral drugs by liquid chromatography [257].

Several examples of recently published enantioseparations of different drugs in human body fluids and relevant chromatographic conditions are presented in Table 3.

These data may be supplemented by HPLC determinations of enantiomers of: 3-amino-2-fluoropropylphosphinic acid (GABA receptor agonist) in plasma [291], N-ethyl-3,4-methylenedioxyamphetamine and its major metabolites in plasma and urine [292], modafinil in serum [293], arotinolol in plasma [294] and methadone and its metabolite in saliva [295]. HPLC determination of dipiperidon (local anaesthetic) enantiomers in blood serum on a teicoplanin CSP was used for studies of their enzymatic hydrolysis in plasma and it was found that the rate constants for this process were different [296].

The enantiomers of following chiral drugs were determined in rat body fluids using HPLC: in plasma: fluoxetine [297], propranolol [298], N-(4-chlorophenyl)-1-(4-pyridyl)ethylamine (novel anticonvulsant) [299], alprenolol [300] and azelastine and its metabolites [301]; in serum: ibuprofen [302] and flurbiprofen [303]; in urine: 3,4-methylene-N-methylbutanamine (new street drug) [304] and in plasma and urine: XK469 (new antitumor agent) [305]. Enantiomers of ofloxacin [306] and oxazepam [307] were assayed by enantioselective HPLC in rabbit plasma, whereas a novel antibacterial nonfluorinated quinolone, PGE-9509924, was similarly determined in dog plasma [308].

Table 3. Enantioseparations of Different Drugs in Human Body Fluids and Relevant Chromatographic Conditions

Chiral drug	Body fluid	Chromatographic conditions (method, column/CSP, mobile phase/carrier gas, detection)	Reference
Albuterol	p	HPLC, Chirobiotic T, CH ₃ OH:CH ₃ COOH:28% (v/v)NH ₃ 1000:5:1 (v,v,v), MS	[258]
Amlodipine	p	HPLC, Chiral AGP, 10 mM acetate buffer (pH 4.5)-1-propanol (99:1, v/v), MS	[259]
Atenolol	p, u	HPLC, Chiralcel OD-H, hexane-ethanol (85:15, v/v) + 0.1% DEA, F.	[260]
Baclofen	p	HPLC, Chirex 3216, 0.4mM CuSO ₄ in CH ₃ CN-20mM acetate buffer (pH 5.5) (17:83, v/v), UV	[261]
Carvedilol	p	HPLC, teicoplanin, CH ₃ OH-CH ₃ CN-triethylammonium acetate (70:30:0.05, v/v/v), F	[262]
	s	HPLC, (S)-indoline-2-carboxylic acid + (R)-1-(<i>n</i> -naphthyl)ethylamine, hexane:dichloromethane:ethanol (50:35:15, v/v/v) and 0.25% (v/v) CF ₃ COOH, F	[263]
Chlorpheniramine ¹	p	HPLC, -cyclodextrin, 0.25% DEA acetate (pH 4.4)- CH ₃ OH- CH ₃ CN (85:7.5:7.5, v/v/v), MS	[264]
Ethosuximide	p, u	GC, 25QC2/CYDEX- , helium, MS	[265]
Felodipine	p	HPLC, Chiralcel OJ-R, 2-propanol-2-methylpentane (11:89 v/v), MS	[266]
Fluoxetine and norfluoxetine	p, s	GC, heptakis(2,3-di-O-methyl-6-O-tert-butyldimethylsilyl)- -cyclodextrin in OV 1701, hydrogen, N/P selective detector	[267]
	p	HPLC, Chiralcel OD-R, 100 mM KPF ₆ - CH ₃ CN (65:35, v/v), UV	[268]
Flurbiprofen ¹	p, u	HPLC, Chiralpak AD, hexane-ethanol (87:13, v/v) and (90:10, v/v) for p and u, respectively + TFA (0.05%, v/v), UV, F	[269]
Ibuprofen	p	HPLC, Chiralpak AD-RH, CH ₃ OH-H ₂ O (8:2, v/v) + 0.1% H ₃ PO ₄ , MS	[270]
Ketamine and norketamine	p	HPLC, Chiral AGP, 2-propanol-10nM ammonium acetate buffer (pH 7.6) (6:94, v/v), MS	[271]
Lercanidipine	p	HPLC, Chiralpak AD, hexane-ethanol-DEA (95:5:0.1), MS	[272]
Loxoprofen	p	HPLC Chiralcel OJ, hexane-2-propanol-TFA (95:5:0.1, v/v/v), UV and CD	[273]
Mephénytoin	u	GC, Chirasil-Val, helium, MS	[274]
Mephénytoin ¹	p	HPLC, Chiral AGP, 2.5% CH ₃ CN in phosphate buffer (pH 7.0), UV	[275]
Metoprolol	u	GC, derivatization with N-methyl-N-(trimethylsilyl)trifluoroacetamide and (-)- -methoxy- - (trifluoromethyl)phenacetyl chloride, helium, MS	[276]
Omeprazole ¹	p	HPLC, Chiralpak AD-RH, 20 mM phosphate buffer (pH 4.65)- CH ₃ CN (70:30, v/v), CD, MS	[277]
Omeprazole	p	HPLC, Chiralpak AD, ethanol-hexane (70:30 v/v), UV	[278]
	p	HPLC, amylose tris(3,5-dimethylphenylcarbamate), CH ₃ CN-H ₂ O (60:40, v/v), UV	[279]
Pantoprazole		HPLC, amylose tris(3,5-dimethylphenylcarbamate), CH ₃ CN-H ₂ O (35:65, v/v), UV	[280]
Pindolol	s, u	HPLC, phenylcarbamate -cyclodextrin,), CH ₃ CN-H ₂ O (50:50, v/v) containing 10 nM ammonium acetate MS	[281]
Pirlindole	p	HPLC, Chiralcel OD-R, 50 mM phosphate buffer containing NaClO ₄ (50 mM) (pH 5.0)-CH ₃ CN (65:35, v/v), F	[282]
Pyridoglutethimide	s	HPLC, Chiralcel OD-R, CH ₃ CN-0.3 M aqueous sodium perchlorate (pH 6.2), UV	[283]
Reboxetine	s	HPLC, Chiral AGP, 25% CH ₃ CN in 10mM ammonium acetate (pH 5.1), MS	[284]
Sotalol	p	HPLC, cellobiohydrolase I (Chiral CBH), 15% 2-propanol in 10 mM phosphate buffer (pH 7.0) containing 0.05 mM EDTA, F	[285]
	p	HPLC, teicoplanin, CH ₃ OH- CH ₃ CN-CH ₃ COOH-TEA, MS	[286]
Terbutaline	p	HPLC, Chirobiotic T, 0.1% ammonium trifluoroacetate in CH ₃ OH (w/v)- CH ₃ OH (90:10, v/v), MS	[287]
Tramadol and O-desmethyltramadol	p, u	HPLC, Chiralpak AD, 2-methylpentane-ethanol-DEA (97:2.8:0.1, v/v/v), F	[288]
Warfarin	p	HPLC, ovomucoid, 0.05 M ammonium acetate (pH 4.7)- CH ₃ CN (90:10, v/v), F	[289]
Zopiclone ¹	p	HPLC, Chiralcel OD-H, heptane-ethanol (2:3, v/v), UV	[290]

Abbreviations: p - plasma, u - urine, s - serum, MS - mass spectrometry, DEA - diethylamine, F - fluorescence, TFA - trifluoroacetic acid, CD - circular dichroism, EDTA - ethylenediaminetetraacetic acid, TEA - triethylamine, ¹ and metabolites

Enantioselective HPLC chromatographic methods are used for determinations of chiral metabolites of drugs, such as enantiomers of: 11-dihydrooracin (metabolite of potential cytostatic drug – oracin) [309], metyrapol (metabolite of metyrapone – diagnostic test agent for pituitary-adrenal function) in human plasma [310] or acidic metabolite of metoprolol in plasma and urine [311]. Enantiomers of albendazole sulfoxide (metabolite of anthelmintic albendazole) were resolved by supercritical fluid chromatography on Chiralpak AD and Chiralcel OD columns [312]. Many of the above mentioned enantioselective determinations of drugs and their metabolites were used for pharmacokinetic studies.

Important chromatographic enantioseparations deal also with drug candidates and compounds of defined biological activity and endogenous biochemicals. They may be represented by HPLC resolutions of enantiomers of chiral sulfoxide using Chiralpak AD, 2-propanol-hexane (80:20, v/v) mobile phase and MS detection [313], enantiomers of: 4-aryl-7,7-dimethyl- (and 1,7,7-trimethyl-)1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-diones [314] and -2,5-thiones [315] (potential calcium antagonists), bioactive cyclic Mannich ketones (potential antibacterials) [316], azole antifungal agents [317], 2-arylindoles (5HT_{2A} receptor antagonists) [318], chiral cannabinol receptor ligand [319], new chiral hydantoin derivatives [320], tetralone derivatives (17 - hydroxylase/17,20-lyase inhibitors) [321], 2,3-dihydro-1,2,5-benzothiadiazepin-4(5H)-one and thione 1,1-dioxides (potential anti-AIDS chemotherapeutic agents) [322] and chiral dihydrofurocoumarins [323]. Coupled column HPLC was used for separation and assay of enantiomers of alkoxy-substituted esters of phenylcarbamic acid in serum [324].

Diastereomeric and enantiomeric HPLC resolutions were reported for nucleoside analogs (potential antiviral agents) [325-327]. Uracil dinucleoside was synthesized and its enantiomers were separated by enantioselective HPLC on - cyclodextrin column [328]. Enantioseparation of the key intermediate of paroxetine (antidepressant) was accomplished on three polysaccharide-based CSPs [329].

Last but not least, recent enantioseparations of drugs in dosage forms should be mentioned. They are exemplified by HPLC resolutions of troglitazone (oral antidiabetic drug) stereoisomers on Chiralcel OJ-R column and their determination in tablets [330]. Also in tablets enantiomers of aminoglutethimide (drug used in the treatment of hormone dependent metastatic breast cancer) were determined by HPLC as dansyl and fluorescamine derivatives [331]. Enantiomers of flurbiprofen were assayed in sustained release capsules by HPLC on (3S,4S)-4-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydrophenanthrene CSP (Whelk-O 1) [332]. It is worth to note that a majority of the above mentioned HPLC enantioseparations were accomplished on the polysaccharide CSPs and that the mass tandem spectrometry is more and more frequently used for detection.

4.3. Enantioseparations of other Compounds

Quite close to the enantioselective analysis of drugs is the resolution and determination of enantiomers of chiral compounds of natural origin. Important from the medical

point of view may be GC-MS enantioselective analysis of chiral urinary metabolites (mainly hydroxyacids) useful in the diagnosis of peroxisomal diseases [333], LC-MS determination of glyceric acid enantiomers in urine as markers of glyceric acidurias [334] and enantiomeric separation of 3-hydroxybutyrate on Chiralcel OD-RH column [335]. Measurement of lactic acid enantiomers as indicators of metabolic acidosis was recently excellently reviewed [336].

Gas chromatographic determination of the ratio of arabinitol enantiomers in urine samples (that constitutes a marker of disseminated candidiasis) was accomplished with -cyclodextrin CSP and electron capture and MS detection [337].

Enantioselective analysis of chiral compounds of plant origin may be exemplified by studies on: GC chiral recognition of terpenoids in some pharmaceuticals derived from natural sources [338], GC enantiomeric analysis of linalool in essential oil [339], enantioseparation of monoterpenes commonly present in citrus [340], enantiomeric purity of odorants in Chinese jasmine green tea scented with flowers of *Jasminum sambac* [341], HPLC determination of synephrine (adrenergic agonist) enantiomers in plant material [342], enantiomeric composition of filbertone in hazelnut oils [343], enantioselective GC-olfactometry analysis of lilac aldehyde and lilac alcohol stereoisomers [344], determination of benzophenanthridine alkaloids from methanol extracts of *Hylomecon* species [345] and chiral analysis of lignans from various plant sources [346-349]. Comprehensive two-dimensional gas chromatography was applied in the determination of enantiomeric distribution of some monoterpenes in bergamot essential oil and advantages of this method were discussed [350].

Recent literature reports also enantioseparations of different classes or individual representatives of organic chiral compounds. For instance, a set of 111 chiral compounds (with many drugs, and amino acids) was submitted to enantioseparations on macrocyclic glycopeptide CSPs (teicoplanin, its aglycone and ristocetin) with supercritical and subcritical mobile phases [351]. The performance of these CSPs were compared and the first two showed the best results. The speed of separations was the main advantage of supercritical enantioseparations compared to those by normal-phase HPLC. Enantiomers of many sulfoxides were resolved by HPLC on macrocyclic glycopeptide CSPs [352], native and derivatized cyclodextrin CSPs [353] and polysaccharide-based CSPs [354]. Enantiomers of chiral sulfoxides and sulfinic acid esters were also resolved on four derivatized cyclodextrin CSPs using gas chromatography [355] and the same type of chromatography was used for enantiomeric analysis of selenomethionine in food supplements and urine [356] and enantioseparations of -butyrolactone derivatives [357]. Enantiomers of diphosphine and diphosphine oxide ligands were resolved by HPLC on four different CSPs [358], whereas enantiomers of amines, amino alcohols and related compounds were separated by HPLC on crown ether CSP [359]. Cyclodextrins as mobile phase additives enabled enantioseparation of some mandelic acid esters [360]. Chiral aminoacetonitriles and diamines were enantioseparated by HPLC on (R)-3,5-dinitrobenzoylphenylglycine CSP [361] and enantiomers of chiral meta-substituted diphenylmethanols were separated by

indirect mode HPLC after derivatization with chiral phthalic acid derivative and enantiomers of 2-methoxy-2-(1-naphthyl)propionic acid [362]. Two cellulose-based CSPs (Chiralcel OD and OF) were used for HPLC enantioseparations of pyrethroic acid esters [363]. Some peptide enantiomers were resolved by cinchona alkaloid derived CSP and the mechanism of chiral recognition was studied by NMR and molecular modeling methods [364,365]. HPLC enantioseparations were also reported for Wieland-Miescher ketone and three related compounds [366], trans-2-aminocyclohexanol [367] and novel chiral tetrahedrane-type clusters [368,369]. Separation of enantiomers (and geometrical isomers) of some furan derivatives was studied by GC-MS, supercritical fluid chromatography and HPLC on different CSPs [370]. GC enantioseparations on α -cyclodextrin derivative CSP (Chirasil-DEX) were compared with those by HPLC on S,S-ULMO chiral column for many aryl- and heteroarylcarbinols [371]. Planar chromatography on tribenzoylcellulose was used for quantitative densitometric determination of four chiral alcohols (tiochroman-4-ol, benzoin, α -methylbenzoin and anisoin) [372].

5. APPLICATIONS OF ENANTIOSELECTIVE CHROMATOGRAPHY

Several applications of enantioselective chromatographic methods were already mentioned. The broadest field is represented by studies on stereoselective pharmacokinetics of chiral drugs and their metabolites in living organisms, mainly in humans, and stereoselective interactions of drugs with receptors. Several recent reviews and reports dealing with these subjects are presented in Table 4. Applications of enantioselective HPLC chromatography to studies on stereoselective fate of different drugs may be exemplified by investigations on: metabolism and pharmacokinetics of ibuprofen (indirect mode, derivatization with (R)-1-naphthen-1-yl)ethylamine, and direct mode on Chiralpak AD and Chiralcel OD columns) [382] or influence of age on the enantiomeric disposition of this drug in healthy volunteers

(indirect mode as above) [383], pharmacokinetics of BOF-4272 (xanthine oxidase inhibitor) in rats and dogs (Chiralcel OD column) [384] and metoprolol (teicoplanin CSP [385] and Chiralpak AD column [386]), metabolism of flufenen in human hepatocytes (Chiralcel OD-R column) [387] or in guinea pigs (1-allyl tergeride column) [388], metabolism of pentoxifylline (hemorheological agent) (cellobiohydrolase column for preparative enantioseparation of chiral metabolite and indirect mode after its derivatization with diacetyl-L-tartaric acid) [389], disposition of venlafaxine (antidepressant) enantiomers in rats [390], pharmacokinetics of nefopam (analgesic) and desmethylnefopam [391] (for both vancomycin CSP and MS detection) and metabolism of citalopram (antidepressive) enantiomers in CYP2C19/-CYP2D6 phenotyped panels of healthy Swedes (Cyclobond I 2000 column) [392].

Chromatographic enantioseparations found applications in solving different problems of agriculture and food industry. Only recent results may be mentioned here, like studies of : wine malolactic fermentation (use of multidimensional enantioselective GC-MS with 2,3-di-O-methyl-6-O-tert-butylidimethylsilyl)- α -cyclodextrin as chiral selector for determination of ethyl lactate and other chiral compounds enantiomeric ratios) [393], assesment of authenticity of fruit beverages [394] and changes in volatile compounds of carrots during refrigerated and frozen storage [395] (in both GC enantioseparations of different terpenes on α -cyclodextrin derivatives CSPs), discrimination between Arabica and Robusta coffee species on the basis of their amino acid enantiomers (GC enantioseparations on Chirasil L-Val column) [396] and HPLC separation of diastereomers of narangin in grapefruit during maturation (Chiralcel OD column) [397].

Enantioselective chromatography also assists environmental protection in determinations of enantiomers of different environmental pollutants like pesticides, insecticides etc. Recent examples are represented by studies on: quantification of hydrolysis-induced racemization of amino acid enantiomers in environmental samples (GC-MS on

Table 4. Representative Recent Reviews and Reports Dealing With Drug Chirality

No.	Title	Ref.
1.	Drug chirality in anesthesia	[373]
2.	Impact of stereoselectivity on the pharmacokinetics and pharmacodynamics of antiarrhythmic drugs	[374]
3.	Enantioselective analytical methods in pharmacokinetics with specific reference to genetic polymorphic metabolism	[375]
4.	Enantiomer's potential in psychopharmacology - a critical analysis with special emphasis on the antidepressant escitalopram	[376]
5.	Enantioselective metabolism of the designer drugs 3,4-methylenedioxyamphetamine ('ecstasy') and 3,4-methylenedioxyethylamphetamine ('eve') isomers in rat brain and blood	[377]
6.	Stereochemistry and drug efficacy and development: relevance of chirality to antidepressant and antipsychotic drugs	[378]
7.	Drug testing in blood: validated negative-ion chemical ionization gas-chromatographic-mass spectrometric assay for determination of amphetamine and methamphetamine enantiomers and its application to toxicology cases	[379]
8.	Enantioselective interactions of dextromethorphan and levomethorphan with the α 3-4-nicotinic acetylcholine receptor: comparison of chromatographic and functional data	[380]
9.	Stereostructure-activity studies on agonists at the AMPA and kainate subtypes of ionotropic glutamate receptors	[381]

Chirasil L-Val) [398], enantioselective separation and transformation of the polycyclic musk fragrances in fish and water (GC on β -cyclodextrin derivative CSP) [399], determination of gossypol and gossypolone enantiomers in fish tissues [400,401], biodegradation of metalaxyl (a fungicide) in soil and sunflower plants (HPLC, Chiralcel OJ column) [402,403], determination of epoxiconazole (a fungicide) enantiomers in water and soil (HPLC on microcrystalline cellulose triacetate CSP) [404], separation of enantiomers of polybrominated biphenyls in a technical mixture (HPLC and GC on β -cyclodextrin derivatives CSPs) [405], determination of phenthoate (insecticide) enantiomeric ratio in soil (HPLC, Chiralcel OD column) [406], separation and toxicity of enantiomers of organophosphorus insecticide leptophos (HPLC on Whelk-O 1 CSPs) [407], separations of enantiomers of triadimefon and triadimenol (triazole pesticides - supercritical fluid chromatography on Chiralpak AD column) [408] and those of tebuconazole (antifungal agent) and its impurities (HPLC on aminopropylated silica gel coated with cellulose tris-3,5-dimethylphenylcarbamate) [409], as well as determinations of enantiomeric fractions and tissue distributions of polychlorinated biphenyls and other organochlorine pollutants in seals [410,411] and in human tissues (enantioselective GC on β -cyclodextrin derivatives CSPs) [412]. Six chiral pesticides and related intermediates were enantioresolved on polysaccharide CSPs [413].

Enantioselective chromatography is one of the methods useful for studies on drug-protein binding. Recent examples represent investigations on binding of enantiomers of indobufen to human serum proteins [414], benzodiazepine and coumarin drugs to serum albumin from human and six mammalian species [415] and oxybutynin [416] and desoxybutynin [417] to plasma proteins.

The HPLC analysis of propranolol enantiomers using β -acid glycoprotein CSP was used for studies on stereoselective release of this drug from formulations containing imprinted bead matrices [418], whereas indirect HPLC assay of ketoprofen enantiomers served for determinations of their release from sustained release formulations containing hydroxypropylmethylcellulose [419].

More chemically-oriented applications of enantioselective chromatography deal mainly with separations of products of asymmetric syntheses and determinations of their enantiomeric excess and absolute stereochemistry. These concern such compounds as 2-amino-3-(3-hydroxy-1,2,5-thiadiazol-4-yl)propionic acid (glutamate receptor ligand -preparative and analytical HPLC on crown ether CSP [Crownpak CR(+) and CR(-) columns]) [420], diene epoxy monomers (HPLC on Chiralcel OJ column and GC on ALPHA DEX capillary column) [421], indole 3-succinic acid (auxin - HPLC on Cyclobond I 2000 column) [422], 1,1,1,3,3-pentafluoro-2-(fluoromethoxy)-3-methoxypropane (capillary GC on β -cyclodextrin derivative CSP - Lipodex E) [423], 2,3,3',4',5,5'-hexachloro-1'-methyl-1,2'-bipyrrole (GC on permethylated β -cyclodextrin CSP) [424], 1-(thi)oxo-thiazolanyl-3-(thi)oxothiazolanyl toluene atropoisomers (HPLC on polysaccharide CSPs) [425], (-)-blestriarene C (a biphenanthrene derivative - preparative enantioselective HPLC on Chiralpak AD) [426], trans-,9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid (HPLC on Kro-masil CHI-

DMB column) [427], (+)-quinolizine 207I (GC with β -cyclodextrin-based CSP) [428], β -substituted β -butyrolactones (HPLC on Chiralcel columns) [429], products of asymmetric reduction of fluorour ketone analogues [430] and O-acetylmandelate and ibuprofen amide [431] (HPLC with Chiralcel OD-H and β -cyclodextrin-based columns).

Further examples deal with tangutorine (indole alkaloid, HPLC on Chiralcel OD and Chiralpak AD CSPs) [432], products of enantioselective enzymatic hydrolysis of 2-aryloxyalkanoic acid methyl esters (HPLC on penicillin G acylase CSP) [433], 2-amino-4-phenylbutanoic acid (HPLC on teicoplanin CSP) [434], O,O-dialkyl-2-benzyloxycarbonylaminoarylmethyl-phosphonates (HPLC on cellulose [435] and amylose [436] tris(3,5-dimethyl-phenylcarbamate) CSP and chromenone benzoxazole receptor for glutamic acid and its derivatives (racemic mixture resolved on TLC plates impregnated with (R,R)-thiodilactic acid) [437].

Another important application of enantioselective chromatography is associated with determination of enantiomerization barrier of compounds, mainly those important from the medicinal point of view. The subject of determination of the interconversion energy barrier of enantiomers by separation methods in the last 20 years was recently excellently reviewed [438]. The newest experimental papers report determinations of enantiomerization barriers for such compounds as dialkyl-1,3-allene dicarboxylates [439], thalidomide [440] and some β -nitroketones [441] by enantioselective GC on β -cyclodextrin derivative columns. HPLC CSPs were also used for the same purpose for *o*-dinaphthylphenyl derivative (Chiralcel OD column) [442], aryl oximes Chiralcel OD and Chiralpak AD columns) [443], carbethoxy-1,4-benzodiazepin-2-one (N-3,5-dinitrobenzoyl- L-phenylglycine and L-leucine CSPs) [444], 5-arylthiazolidinedione derivative (peroxisome proliferator-activated receptor agonist - preparative and analytical enantioseparations on Whelk-O CSP, racemization in dog and human plasma) [445], CC-4047 (amino-substituted analog of thalidomide - immunomodulatory drug in clinical development - Chiralpak AD CSP, racemization in human plasma and phosphate-buffered saline) [446], chiral barbituric and thiobarbituric acids (Chiralcel OD-H column) [447] and 2-carboxy-2'-methoxy-6-nitrobiphenyl (Chiralpak AD column) [448]. A mathematical-analytical equation for determination of mobile phase rate constants for enantiomerization gave very good agreement with experimental enantioselective HPLC results (ChiraDex column) for oxazepam enantiomerization [449].

New contributions of enantioselective chromatography in the field of combinatorial chemistry may also be mentioned [450-452].

6. MISCELLANEOUS

A few papers do not fit exactly in the above presented paragraphs but deal with chromatographic enantioseparations. A review was published on reversal of elution order during the chiral separation by HPLC [453]. Experimental papers describe enantioseparations of tryptophan and thiopental using membrane chromatography with bovine

serum albumin as a chiral selector [454], separation of 1,1'-bi-2-naphthol enantiomers through achiral chromatography [455] and comparative separation of enantiomers of the same compound and 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate by HPLC and capillary electrophoresis to investigate chiral recognition of single and dual combined chiral selectors [456]. Franco *et al.* [457] reported enantiomer separation of N-derivatized amino acids and 2-aryloxypropionic acids by countercurrent chromatography using cinchona-derived anion-exchange-type chiral selectors, whether the most interesting and future-oriented paper dealt with studies on methods of amino acids derivatization for GC-MS assays which may be used in future space and especially Mars exploration missions [458].

7. CONCLUSION

The material presented above clearly demonstrates that enantioselective chromatography in recent years is further expanding its methodology, usefulness and multidimensional applications. One can expect that these trends will continue in the future.

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