Recent Developments in Chiral Stationary Phases: A Mini-Review

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ABSTRACT

The purification of racemic drugs into enantiopure drugs is an extreme demand of the pharmaceutical industry. In racemic drugs, two or more enantiomers are often present. In these isomers, one isomer may be pharmacologically active whereas another isomer(s) may be inactive or in teratogenic (toxic) form. The resolution of pharmacologically active isomer from inactive or teratogenic isomer is an extreme need. As a result, the development of resolution techniques to obtain the enantiopure drug is very essential to treat the disease. In the present review, recent developments of different chiral stationary phases (CSPs) such as pirkle, polysaccharides and polypeptides, inclusion, ligand-exchange, macrocyclic antibiotics, and miscellaneous CSPs in a resolution of racemic drugs/mixtures are discussed. The progress of these CSPs in high performance liquid chromatography (HPLC), gas chromatography (GC), capillary electrophoresis (CE), supercritical fluid chromatography (SFC), and simulated moving bed (SMB) chromatography is discussed. Different interactions between CSPs and analytes which attributes for resolution of racemic drugs are also discussed.

Key Words: *Racemates, Racemic drugs, Chiral separation, Enantiopurification, Chiral stationary phases*

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INTRODUCTION

The mixture of two or more enantiomers wherein one enantiomer may be pharmacologically active and another enantiomer(s) may be equal/less potent, inactive, or toxic can be referred to as a Racemate. Over the past few decades, drugs were used in the form of a racemate to treat the diseases. The thalidomide tragedy first time underlined the importance of drug resolution [1]. In this tragedy, due to the presence of toxic isomer along with pharmacological isomer, 10000 children were born with phocomelia congenital disorder. Indeed, each enantiomer in the racemate is selective toward the pharmacological effect. Therefore, the resolution of racemates into enantiopure drugs by different resolution techniques is important and is a demand in organic and pharmaceutical chemistry [2]. The significance of chirality in drug design and development is discussed in the literature [3].

In some cases, synthesis of enantiopure molecules is not possible since enantiopurity of the product depends on regio-, chemo- and stereo-selectivity of the chiral catalysts, reagents, substrates, or other chiral entities [4-12]. Therefore, synthesis of the racemate and subsequent resolution is needed. Different methods such as chiral catalysis, chiral pool, chiral reagent, asymmetric synthesis (chiral substrate and chiral auxiliary) [7-11], crystallization [13], and resolution (direct and indirect) are the ways to obtain enantiopure molecules [14, 15]. The optical purity of enantiopure molecules can be determined by an enantiomeric excess which can be examined by different analytical techniques such as chromatographic, spectroscopic, light, and thermal methods. The analytical techniques such as gas chromatography (GC) [16], supercritical fluid chromatography (SFC) [17], simulated moving bed (SMB) chromatography [18], high performance liquid chromatography (HPLC) [19], capillary electrophoresis (CE) [20], thin layer chromatography (TLC) [21], nuclear magnetic resonance (NMR) [22], circular dichroism (CD) [23], X-ray diffraction [24], isotopic dilution (ID) [25], differential scanning calorimetry (DSC) [26], polarimetry [27], and some miscellaneous methods [28] are available for optical purity (enantiomeric excess) determination. Some of them are useful for analytical (qualitative) purposes and some

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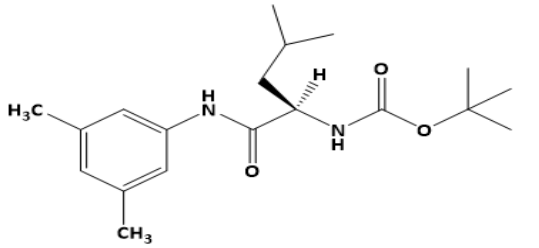
are related to the large and industrial scale (quantitative) resolution. Most of the chromatographic methods used the chiral mobile phase additives (CMPAs) and chiral stationary phases (CSPs) for enantioseparation. In the present review, we have discussed the recent developments in different types of CSPs.

Chiral stationary phases

In general, direct and indirect resolution techniques are useful for the resolution of the racemates. Owing to an expensive chiral substrate, reagent, and catalysts (required to obtain enantiopure compounds/drugs), the indirect resolution method is rarely used compared to the direct resolution method. In a direct resolution, CSPs and CMPAs are two different methods of resolution. However, due to several variable parameters (large availability of CSPs, diversified mobile phase, and wide applicability), CSPs are potentially used compared to the CMPAs [29, 30]. In the present review, different types of CSPs such as pirkle, polysaccharides and polypeptides, inclusion, ligand-exchange, macrocyclic antibiotics, and miscellaneous CSPs are discussed in detail.

Pirkle type

William Pirkle is a pioneer of the brush (π-donor–π-acceptor) type of CSP therefore also known as Pirkle brush CSP [31]. In brush-type CSPs, chiral selectors are small molecules which densely arrayed on the surface of silica or other adsorbent materials. The interactions such as π-π (acidic/basic) interaction and steric (repulsive) interaction which attributes of Pirkle type of CSPs. In addition, dipole interaction and intermolecular hydrogen bonding are also attributed to chiral recognition in Pirkle CSPs. Aromatic rings are a potential source of π-π electrons and acidic sites that offers intermolecular hydrogen bonding. This CSP is based on the formation of three-point interaction between a chiral selector (CSP) and an analyte. An analyte that forms three-point interaction with a chiral selector retains for a longer period, whereas another analyte that forms a one- or two-point interaction elutes faster. Brush-type CSPs are robust and long-lived due to covalent attachment with chromatographic support. The robustness of CSPs offers the use of a wide variety of mobile phases which is useful for less soluble analytes. The hydrophilic and hydrophobic nature of the supported chiral selector significantly affects the resolution. Forjan *et al.* [32] obtained the new brush-type CSP for HPLC which comprises π-acidic N-(3,5-dinitrobenzene)-D-α-phenyl glycine chiral units linked to the quinoxaline of modified γ-aminopropyl silica gel using a spacer (1,2-diaminoethane) by solid-phase synthesis. They resolved 22 racemates due to hydrogen bonding and π-donor–π-acceptor group interactions between CSP and an analyte. The obtained CSP has a broad range of applications to resolve the racemates. Kontrec *et al.* [33] used the chiral Pirkle-type of CSP containing 4-chloro-3,5-dinitrobenzoic acid (CDNB) and 2,4,5,6-tetrachloro-1,3-dicyanobenzene (TCDCB) as branching unit. Çakmak *et al.* [34] prepared a pirkle-type CSP from aromatic amine derivative of (*R*)-2-amino-1-butanol as a chiral selector and was used for enantioseparation of mandelic acid and 2-phenyl propionic acid which shows enantiomeric excess of 60.8% and 27.4%, respectively. In addition, enantioselective interactions between the prepared CSP and analytes were also studied by docking, molecular dynamics simulation, and quantum mechanical computation methods. Levkin *et al.* [35] discussed enantioselective and non-enantioselective interactions of racemic compounds with brush-type of CSPs in liquid chromatography. Recently, Knezevic *et al.* [32] discussed new brush-type CSPs for enantioseparation of different pharmaceutical drugs including ibuprofen, ketoprofen, naproxen, flurbiprofen, suprofen, fenoprofen, lorazepam, oxazepam, temazepam and so on. Aboul-Enein *et al.* [36] resolved racemic drugs with two stereogenic centers including formoterol, labetalol, nadolol, indenolol, and U-54494A by HPLC using Pirkle-type CSPs. The screening and use of various kinds of pirkle-type CSPs for enantioseparation are discussed in the literature [37]. The common pirkle-type (π-donor-π-acceptor) compounds and CSPs [38] are shown in **Figure 1**.



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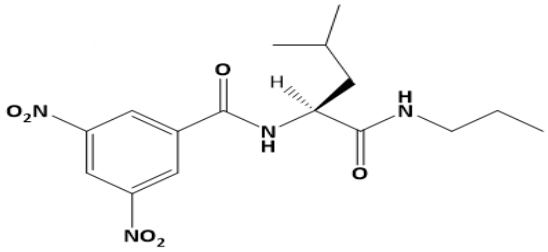

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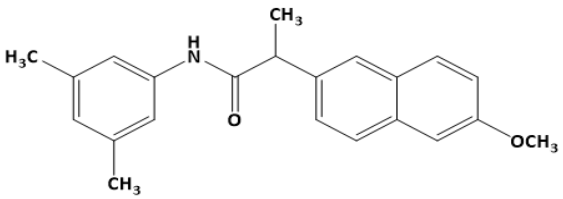

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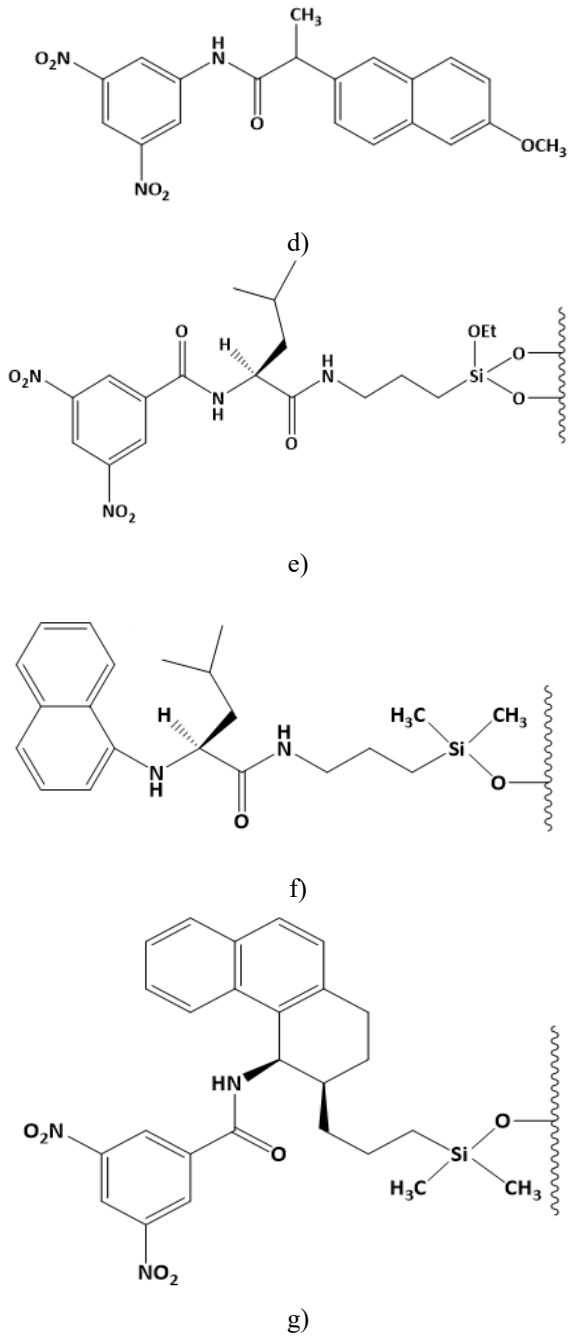
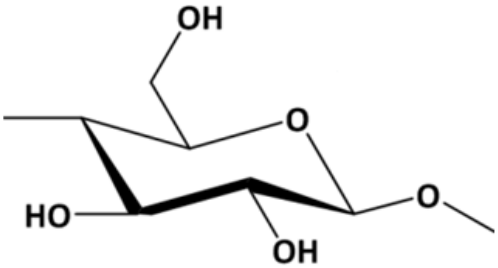


Figure 1. Pirkle type (π-donor–π-acceptor) compounds (a, b, c, and d) and CSPs (e, f, and g)

Polysaccharides and polypeptides

Polysaccharide is a polymer of monosaccharide containing glycosidic bonds. Polysaccharides are versatile chiral selectors and useful in HPLC for analytical and preparative scales. The native polysaccharides (cellulose) are weak in chiral recognition, whereas their derivatives (triacetate, carbamates, and ester) have strong interaction with the racemic analyte. Three well-known polysaccharides are starch, glycogen, and cellulose, which contain glucose as the main unit. The glucose units are linked by β-glycosidic bonds in cellulose and by α-glycosidic bonds in glycogen and starch. Some other polysaccharides like chitin, chitosan, and amylopectin are also useful as chiral selectors. Cellulose has more hydrogen bonds than glycogen and starch. As a result, cellulose and its derivatives are abundantly used as a chiral selector for the resolution of a wide range of chiral compounds. Polysaccharide or their derivatives coated CSPs have a solvent limitation, whereas immobilization allows the use of a wide range of solvents which is increasingly important [39]. Ali *et al.* [40] describe the importance of immobilized polysaccharide CSPs over coated CSPs from the view of the use of solvent flexibility. The immobilization of polysaccharide derivatives provides several advantages such as flexibility in eluent and the injection solvent, higher chiral recognition ability, greater loading capacity, and long life of the column over the coated-type CSPs [41]. Different types of polysaccharide-based CSPs such as CHIRALCEL OB-H, CHIRALCEL OD-H, CHIRALPAK AD, CHIRALPAK AS, and CHIRALCEL OJ, as well as protein-based CSPs such as CHIRAL AGP and ULTRON ES-OVM, are used for enantioseparation. Thunberg *et al.* [42] used the CSPs such as Chiralpak AD, Chiralpak IA, Chiralcel OD and Chiralpak IB for the resolution of 48 different analytes. They observed that most of the racemates showed better resolution on Chiralpak AD-H than on Chiralpak IA. Further, Chiralcel OD-H revealed higher enantioselectivity than Chiralpak IB for most of the racemates. The addition of water as mobile phase additives can improve or prevent enantioseparation which is depending on the type of a column [43]. In 2018, Szabó *et al.* [44] used four different chiral columns (Chiralpak AD, Chiralcel OD, Chiralpak AS, Chiralcel OJ) with 5 different solvents (methanol, ethanol, 1-propanol, 2-propanol, and acetonitrile) at 5 different temperatures (5-40°C) for enantioseparation of an antidiarrheal drug, racecadotril. They observed that all columns except Chiralpak AS showed significant enantioseparation capabilities using alcohol-type solvents over acetonitrile. Further, Ali *et al.* [45] discussed the different chromatographic techniques such as HPC, CE, SFC, and TLC with polysaccharide CSPs. The comparatively discussed the coated and immobilized polysaccharide CSPs. Undoubtedly, immobilized polysaccharide CSPs are superior to coated CSPs and are quite developed. However, immobilized CSPs are not capable of enantioseparation at a preparative scale. Recently, Moldovan *et al.* [46] resolved 16 β-blocker drugs using commercially available four different polysaccharides immobilized CSPs. Moreover, Bajtai *et al.* [47] developed polysaccharide-based CSPs for enantioseparation of natural and synthetic Cinchona alkaloid analogs by liquid chromatography. The structures of various polysaccharides and cellulose derivatives [38] as CSPs are depicted in **Figures 2 and 3**, respectively.



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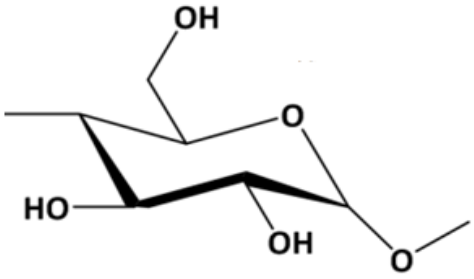

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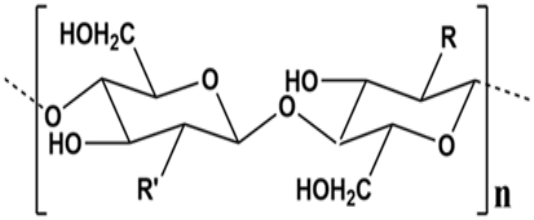

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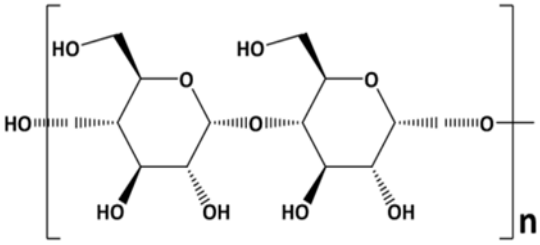

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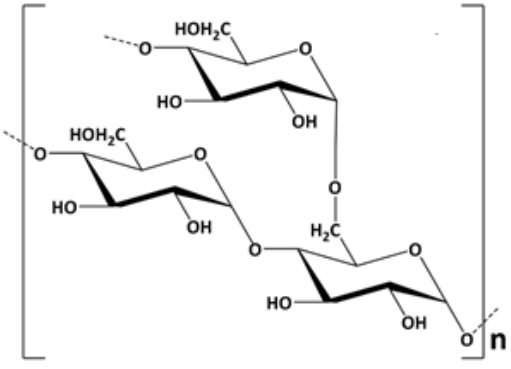

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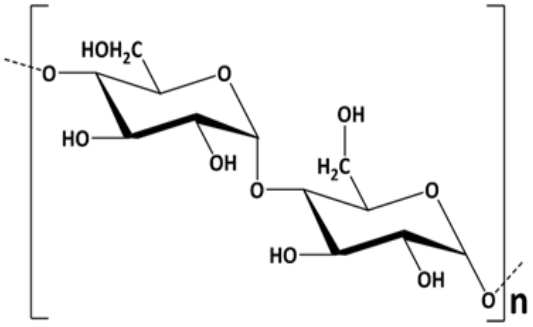

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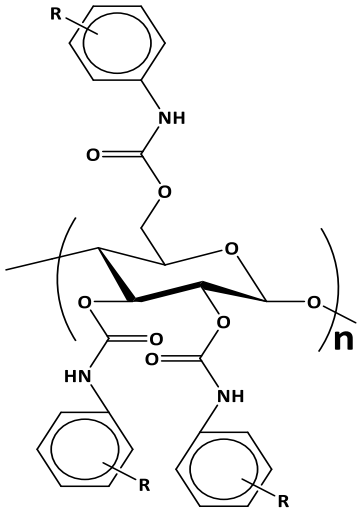
Figure 2. Structures of polysaccharides (a) cellulose (b) amylose (c) chitin (R and R': -$NHCOCH_3$)/chitosan (R and R': -NH_2), (d) maltodextrin, (e) amylopectin, and (f) dextrans and their ester and carbamate derivatives



1. 4-CH_3O, **2.** 4-C_2H_5O, **3.** 4-$(CH_3)_2CHO$, **4.** 4-$(CH_3)_2CHCH_2O$, **5.** 4-$(CH_3)_3Si$, **6.** 4-CH_3, **7.** 4-CH_3CH_2, **8.** 4-$(CH_3)_2CH$, **9.** 4-$(CH_3)_3C$, **10.** 3-CH_3, **11.** 2-CH_3, **12.** H, **13.** 4-F, **14.** 4-Cl, **15.** 2-Cl, **16.** 3-Cl, **17.** 4-Br, **18.** 4-CF_3, **19.** 4-NO_2, **20.** 3,4-$(CH_3)_2$, **21.** 3,5-$(CH_3)_2$, **22.** 2,6-$(CH_3)_2$, **23.** 3,4,5-(CH_3), **24.** 3,5-Cl_2, **25.** 3,4-Cl_2, **26.** 2,6-Cl_2, **27.** 3,5-F_2, **28.** 3,5-$(CF_3)_2$, **29.** 2-Cl-4-CH_3, **30.** 2-Cl-5-CH_3, **31.** 2-Cl-6-CH_3, **32.** 3-Cl-2-CH_3, **33.** 3-Cl-4-CH_3, **34.** 4-Cl-2-CH_3, **35.** 4-Cl-3-CH_3, **36.** 3-F-4-CH_3, **37.** 5-F-2-CH_3, **38.** 3-F-5-CH_3, **39.** 3-Cl-5-CH_3, **40.** 3-Br-5-CH_3.

Figure 3. Cellulose-based derivatives as chiral selectors for HPLC, capillary-liquid chromatography (CLC), and capillary electro-chromatography (CEC)

Like polysaccharides, polypeptides are also widely used for enantioseparation. Proteins are chiral and interact stereochemically with chiral compounds. Proteins form three-dimensional structures during interaction with the enantiomer of a racemic compound and are widely used in HPLC and CE as chiral selectors. An intermolecular multiple hydrogen bonding is one of the important

interaction attributes for chiral resolution. Amino acids and amides-based CSPs were used for the resolution of amino alcohols, amino acids, and hydroxy acids, which are based on the formation of multiple hydrogen bonding. Some stationary phases such as *N*-trifluoroacetyl-L-amino acid esters and valine diamide-linked polysiloxanes were widely used for the resolution of racemate in chiral GC. Recently, Li *et al.* [48] prepared different types of tripeptide CSPs with varying amino acid sequences and terminal groups. They prepared APS-Pro-Val-Phe-NNC (CSP 1) which shows the better resolution of analytes containing π-π interaction(s) and another CSP, APS-Pro-Phe-Val-DNB (CSP 2) shows the better resolution of analytes containing hydrophobic group(s). Both CSPs demonstrated a better resolution capacity for adrenoceptor agonists and analytes containing amide functionality or naphthalene rings. Huang *et al.* [49] prepared seven different types of peptide-based CSPs by varying the number of proline units and length of the spacer with silica gel. They studied the effect of proline unit, spacer length, and mobile phase on the resolution of 53 analytes. Different types of CSPs based on proteins or glycoproteins are also discussed in the literature [50]. In 2016, Zhao *et al.* [51] developed glutathione (GSH)-, somatostatin acetate (ST)- and ovomucoid (OV)-functionalized silica-monolithic CSPs for chiral separation of *dl*-amino acids and drug enantiomers using capillary electrochromatography. These peptides- and protein-silica monolithic CSPs implied their promise for the analysis of metabolic studies as well as drug enantiomers recognition. In addition, the chiral separation ability was significantly improved by modification of AuNPs which results in AuNP-mediated GSH-AuNP-GSH-silica monolithic capillary column.

Inclusion type

An inclusion complex formation is depending on the host-guest interaction and cavity size of the host molecule. The native macrocyclic compounds such as cyclodextrins, calix[*n*]arenes, crown ethers, macrocyclic antibiotics, and their derivatized forms are widely used in chromatographic applications. However, cyclodextrin (CD) is extensively studied in chiral resolution. CD is a cyclic oligosaccharide containing six (α), seven (β), or eight (γ) glucopyranose units. CD can work in both, hydrophilic and hydrophobic environments since the outer part is hydrophilic and the cavity is hydrophobic. CD-based CSPs are more useful than other CSPs. However, β-CD is more powerful than α- and γ-CD. Some small molecules can be resolved by α- and γ-CD. For instance, α-CD is useful to resolve aromatic amino acids and monoterpene hydrocarbons, whereas γ-CD can be used to resolve steroid epimers and polycyclic aromatic hydrocarbons. Mostly, CDs are used in HPLC, GC, TLC, SFC, and CEC. Lai *et al.* [52] derived silica-supported mono (6^A-N-allylamino-6A-deoxy) perphenylcarbamoylated (PICD) α-, β- and γ-CDs via hydrosilylation. They studied the effect of cavity size of cyclodextrin derivative on enantioseparation and concluded that α-PICD can be used for the resolution of flavanone and most aromatic alcohols under normal-phase conditions, whereas β-adrenergic blockers, amines, and non-protolytic compounds can be resolved by α- and β-PICD CSPs. A γ-PICD offers the resolution of sterically encumbered analytes like flavanone compounds under both normal- and reversed-phase conditions. Meng *et al.* [53] demonstrated inclusion phenomena between β-cyclodextrin as a chiral selector and racemic tryptophan. Further, Schurig *et al.* [54] showed enantiomer separation by electrochromatography using modified cyclodextrins as CSP. Recently, Tang *et al.* [55] developed high-performance phenyl carbamate cyclodextrin (CD) clicked CSPs for the resolution of various aryl alcohols and flavonoids. More recently, Zhou *et al.* [56] developed a cationic CD-based CSP via click chemistry for chiral separations in multimode HPLC. The versatility of this CSP was examined by using aromatic alcohols, flavonoids, and isoxazoline enantiomers in both reversed- and normal-phase HPLC. In 2018, Yaghoubnejad and co-workers [57] tested the efficiency of silica-bonded 3-(3,5-dinitrophenylcarbamoyl) deoxycholic acid and silica-bonded (calix[4]arene)-deoxycholic acid for the enantioseparation of *N*-(3,5-dinitrobenzene)-DL-leucine, *N*-(3,5-dinitrobenzene)-DL-valine, omeprazole, diclofop-methyl, DL-mandelic acid and (*RS*)-pregabalin. They showed the active involvement of calix [4]arene-based CSP over 3,5-dinitrophenylcarbamoyl-based CSP. Even today, there is large scope for the application of calix[*n*]arene, crown ethers, macrocyclic antibiotics, and their derivatized forms in the chiral resolution. The structures of different crown ethers, CDs (α-, β- and γ-forms), and chiral BINOL are reported in the literature [58-61]. The mechanism of inclusion complex formation is presented in **Figure 4**.

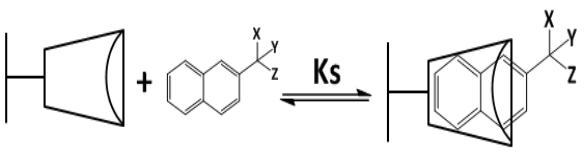
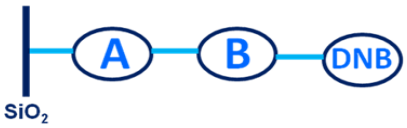


Figure 4. Inclusion of complex formation between CD and an analyte

Ligand exchange

Davankov and Rogozhim invented the term *"Ligand Exchange"*. This technique is based on the formation of mixed metal complexes between a chiral selector and an analyte. The stability is the constant of complexes formed between chiral selectors with *d* and *l* enantiomer often

different attributes for enantioseparation. This is based on the metal complex formation ability of a chiral selector (CMPA/CSP) and an analyte ligand. An ionic interaction between chiral selector and analyte encourages the resolution of the racemate. As per the three-point interaction concept, only ionic interaction is not enough for chiral resolution. Some additional interactions such as dipole-dipole interaction and hydrogen bonding must take part in the resolution [62]. A ligand exchange chromatography (LEC) is based on the formation of labile complexes between transition metal cation and an analyte ligand. In this method, immobilization of cations like Cu(II) or Ni(II) on sulfonic or carboxylic functional groups is useful to form a coordination complex with electron-donating functional groups of an analyte. The analyte forms a stronger complex with metal ions eluted slowly and vice-versa for the analyte which forms a weak complex with metal-ligand of CSP. The principle of LEC is useful in several chromatographic methods such as LC, TLC, GC, CE, and CCLC. The most common application of ligand exchange is developed in GC [63]. ALEC is a simple and inexpensive method and has potential applications in HPLC, CE, and CEC. Due to the complex formation condition, this method has limited applications for the resolution of amino acids, hydroxy acids, dipeptides, diamines, amino alcohols, and their derivatives [63]. Hyun *et al.* [64] synthesized a new silica-supported (*R*)-*N*, *N*-carboxymethyl undecyl phenylglycinol mono-sodium salt for the resolution of α- and β-amino acids and is much better than silica-supported (*S*)-*N*, *N*-carboxymethyl undecyl leucinol mono-sodium salt. They concluded that, obtained CSP is more efficient in the case of resolution factor (Rs) whereas worst in the case of separation factor (α). Oi *et al.* [65] discussed the silica-based different CSPs for gas and liquid chromatography. These CSPs belong to the formation of hydrogen bonds, π-π interaction, and ligand metal complexation. The general structures of ligand exchange CSPs [66] and schematic structures of ligand complex of racemate and metal ion are represented in **Figures 5 and 6**, respectively.



(A: D-Png, D-Val, D-Pro, D-Gln, D-Phe; **B:** D-Png, D-Val, D-Gln, D-Phe, L-Png, L-Val, L-Pro, L-Gln, L-Phe); **OR** (**A:** L-Gln, L-Asn, L-Ser, L-His, L-Asp, L-Arg, L-Glu; **B:** L-Val, L-Leu, L-Ileu, L-Phe, L-Tyr, L-tert-Leu, L-Trp, D-Val, D-Val, D-Leu, D-Ileu, D-Phe, D-Tyr, D-Trp); **DNB:** (3,5-dinitrobenzoyl group). (all D and L compounds mentioned above are amino acids)

Figure 5. The general structure of ligand exchange CSPs

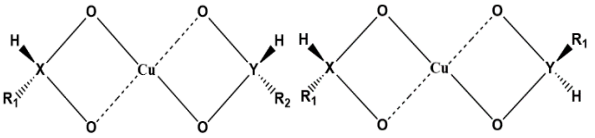


Figure 6. Schematic structures of ligand complex of the racemate and metal ion

Macrocyclic antibiotic

Macrocyclic antibiotics as a chiral selector were introduced by Armstrong. Macrocyclic antibiotics consist of two major classes, namely, ansamycins (rifamycin B and rifamycin SV) and glycopeptides (vancomycin, teicoplanin, ristocetin, and avoparcin). These two types of CSPs are used as chiral selectors in chiral chromatography like HPLC, TLC, CE, and CEC. Out of these CSPs, vancomycin, and teicoplanin are widely investigated and potentially used in chiral chromatography. The structures of the macrocyclic antibiotics (vancomycin, teicoplanin, ristocetin, and teicoplanin aglycon) are quite complicated and reported in the literature [67]. Staroverov *et al.* [68] used the macrocyclic glycopeptide antibiotic (eremomycin) modified silica as a CSP for the resolution of racemic amino acids. ALOthman *et al.* [69] resolved primaquine, quinacrine and tafenoquine antibacterial medicines using ristocetin macrocyclic glycopeptide antibiotics CSP. Teicoplanin is one of the commercially available and widely used CSP in chiral chromatography for enantioseparation of racemic drugs [70]. More recently, a macrocyclic glycopeptide-based column with antibiotic teicoplanin as a chiral selector was used for enantioseparation of ibuprofen, ifosfamide, indoprofen, ketoprofen, naproxen, and praziquantel drugs [71]. They found that teicoplanin demonstrated high linearity, precision, accuracy, and limits of detection in the resolution of these drugs. In the published literature, different types of racemic drugs have been resolved using macrocyclic antibiotics as a CSP [72].

Miscellaneous

In addition to the above five major classes, other CSPs are also discussed. These include chiral surfactants, chiral synthetic polymers, and molecular imprinted polymers (MIPs). Terabe *et al.* [73] introduced the chiral surfactants as a CSP under the name of micellar electrokinetic chromatography (MEKC). A surfactant is a molecule that forms critical micelle concentration (CMC) by a polar head group and a hydrophobic tail. Some common surfactants are long-chain N-alkyl-L-amino acids, N-alkanoyl-L-amino acids, alkyl glycosides, bile salts, saponins, polymeric amino acids, and dipeptide derivatives. *In-situ* polymerization of the chiral monomer with a crosslinker generates chiral synthetic polymer. These types of

polymers may be in the form of powder, pearls, or monoliths and have applications in HPLC and CEC [74]. Polyacrylamide, cellulose triacetate, and their derivatives were extremely used in the resolution of racemic drugs. A ring-opening metathesis (ROM) polymerization is useful for the monolith preparation of chiral synthetic polymers. Sinner *et al.* [75] published the ROM polymerization of norbornene derivatives of β-cyclodextrin for monolith preparation. In MIPs, the synthesis of crosslink polymer in the presence of a chiral template and subsequent removal introduces a chiral cavity in a crosslinked polymer. The generated chiral cavity functions like chiral molecules. This methodology is useful in HPLC, TLC, and CEC. In addition, the properties of different CSPs are tabulated in our recently published review article [76].

CONCLUSION

The purification of racemates into enantiopure molecules is a demand in organic and pharmaceutical chemistry. In the present review, various types of CSPs including pirkle, polysaccharides and polypeptides, inclusion, ligand exchange, macrocyclic antibiotic, and miscellaneous CSPs are discussed with their recent development. Different types of interactions such as π-donor–π-acceptor (acidic/basic), hydrophobic-hydrophilic, steric (repulsive), intermolecular hydrogen bonding, and host-guest type of interaction attributes for chiral separation. The present review is potentially useful to organic, pharmaceutical, medicinal and analytical chemistry researchers.

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