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Imran Ali[a]; Kishwar Saleem[a]; Iqbal Hussain[a]; Vinay D. Gaitonde[b]; Hassan Y. Aboul-Enein[c]
[a] Department of Chemistry, Jamia Millia Islamia New Delhi, India [b] Prochrom India A/2, Varsha Milan, Mumbai, India [c] Pharmaceutical and Medicinal Chemistry Department, Pharmaceutical and Drug Industries Research Division, Dokki, Cairo, Egypt

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Polysaccharides Chiral Stationary Phases in Liquid Chromatography

Imran Ali,[1] Kishwar Saleem,[1] Iqbal Hussain,[1] Vinay D. Gaitonde,[2] and Hassan Y. Aboul-Enein[3]*

[1]Department of Chemistry, Jamia Millia Islamia New Delhi, India
[2]Prochrom India A/2, Varsha Milan, Sahar Road Andheri East, Mumbai, India
[3]Pharmaceutical and Medicinal Chemistry Department, Pharmaceutical and Drug Industries Research Division, National Research Centre, Dokki, Cairo, Egypt

Abstract: Chiral resolution has achieved an independent identity in the separation sciences and polysaccharide CSPs are viewed as effective and efficient CSPs due to their many unique advantages. The present review article highlights the separations of chiral pharmaceuticals and drugs by liquid chromatographic modalities (high performance liquid chromatography, capillary electro-chromatography, sub- and super critical fluid chromatography and thin layer chromatography) utilizing polysaccharide CSPs. Enantiomeric resolution at analytical and preparative scales and a comparison of coated and immobilized CSPs is discussed. The optimization strategies for enantiomeric separation have also been presented. The possible mechanisms of chiral resolution of racemates were also included. The commercial CSPs of all the Companies i.e., Daicel, Kromasil, Macherey Nagel, Knauer and Sepaserve have been compared and discussed. Finally, the role of these CSPs in chiral drugs development programs has also been identified.

Keywords: Chiral separations, polysaccharide chiral stationary phases, analytical and preparative separations, coated and immobilized CSPs, chiral drugs development and xenobiotics

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Address correspondence to Hassan Y. Aboul-Enein, Pharamaceutical and Medicinal Chemistry Department, National Research Cente, Dokki, Cairo 12311, Egypt. E-mail: enein@gawab.com

INTRODUCTION

The importance and utility of enantiomeric resolution started with the discoveries of chirality by Haüy in 1809 (1) and Pasteur's experiments of preferential destruction of tartaric acid by *Penicillium glaucum* (2). Now, it is well established that only one of the enantiomers is pharmaceutically active while the other may be toxic or inactive or ballast. Current government U.S. FDA policy regarding evaluation of drug stereoisomers specify control procedures should be used to assure stereoisomeric composition of a product, with respect to identity, strength, quality and purity. In addition, it is specified that techniques to quantify individual stereoisomers in pharmacokinetic samples should be available early. If the pharmacokinetic profile is the same for both isomers or a fixed ratio between the plasma levels of enantiomers is demonstrated in the target population, an achiral assay should suffice for later evaluations [www.fda.gov/cder/guidance/stereo.htm]. That is why U.S. Food and Drugs Administration and European agencies have banned the marketing of racemic drugs. Only optically active pure forms of racemic drugs are sold into the market due to which the demand of chiral separation methods is increasing continuously. Unfortunately, Asian and African countries are badly suffering by the marketing of racemic drugs leading to various side effects into human body. Optically active drugs, sometimes, racemize leading to toxicity. For example, useful form of (+)-thalidomide converted into harmful (-)-thalidomide *in vitro resulting in to* malformations of embryos in pregnant women (3, 4). Additionally, there are many other examples where chirality plays a crucial role in drug design and development (5–7).

Due to the importance of chirality in human life optically pure active drugs are manufactured either by stereoselective syntheses or chiral separation with feasibility and inexpensiveness of the later method. Therefore, many separation methods have been developed and reported (5, 6). Among these, liquid chromatographic modalities are the choice for this task due to their wide range of applications, ease of operation, selectivities, efficiencies and reproducibilities. In these modalities chiral separations can be achieved either by mobile phase additives or stationary phase approaches. The former approach is not adopted as costly chiral selectors are wasted. On the other hand, later means of chiral stationary phases (CSPs) have been used widely all over the world and about 99 percent chiral separations were carried out by this route. Various chiral selectors have been used to prepare CSPs and most important are polysaccharides, cyclodextrins, macrocyclic glycopeptide antibiotics, proteins, crown ethers, ligand exchangers, Pirkle's types and several others (5, 6). Among these, polysaccharides CSPs are the best due to their high selectivities, sensitivities and reproducibilities (5, 6). Zhang

et al. (8) reported that more than 95% of racemic compounds have been resolved successfully on these CSPs in chromatographic techniques. The use of polysaccharides for chiral separations has been reviewed by a number of workers (9–14). During last few years, significant advances have been made in this area and it is, therefore, time to review polysaccharides CSPs in the chiral resolution of pharmaceuticals and drugs on both an analytical and preparative scale. A comparison of coated and immobilized CSPs was also studied. Finally, possible mechanisms of enantiomeric resolution of racemates were also discussed.

POLYSACCHARIDES AS THE EFFECTIVE AND EFFICIENT CHIRAL SELECTORS

Polysaccharide based chiral selectors are the leaders in the chiral separation science due to their remarkable recognition capabilities (15, 16), which resulted in the chiral separations of many compounds (8). First of all, in 1951, Kotake et al. (17) used cellulose paper for enantiomeric resolution of amino acids and since then polysaccharides have been recognized as potential chiral selectors. The main polysaccharides are cellulose, amylose, chitosan, xylan, curdlan, dextran and inulin (18) but these could not be used as commercial CSPs because of their low resolution capacities and handling problems (19). That is why the derivatives of these polymers were synthesized. Among these, cellulose and amylose approved to be the best polymers because of their good abundance and good capabilities for chiral resolution. Both polysaccharides contain glucose units and a polymeric chains of D-(+) glucose units are joined through β-1,4 and α-1,4 linkages in cellulose and amylose, respectively. The degree of polymerization of cellulose is in the ranges from 200-14,000 units of glucose. Similarly, more than 1000 glucose units are found in amylose. Each glucose unit has chair conformation with 2-OH, 3-OH and 5-CH2OH groups all in equatorial position as shown in Figure 1. The chains of these units lie side by side in a linear fashion in case of cellulose and helical in amylose and, hence, amylose provides more chiral grooves for enantiomeric resolution. Therefore, amylose is better chiral selector in comparison to cellulose (20). The three-dimensional structures of amylose and cellulose are shown in Figure 2 indicating the helical and more defined grooves in amylose than cellulose. As discussed above native amylose and cellulose are not good chiral selectors, and, hence their derivatives were synthesized by different workers (6). Most successful and applicable derivatives of cellulose and amylose are tri-esters and tri-carbamate (18–21).Okamoto et al. in 1984 (22) prepared tri-esters and tri-carbamates of cellulose and amylose and tested them for chiral resolution. Later on, other derivatives of cellulose

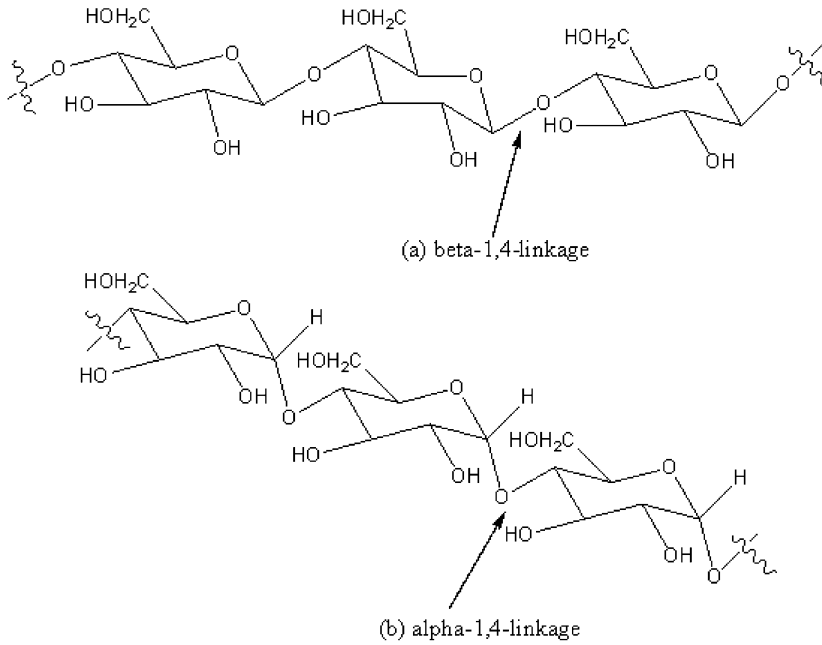


Figure 1. Chemical structures of (a): cellulose and (b): amylose polymers.

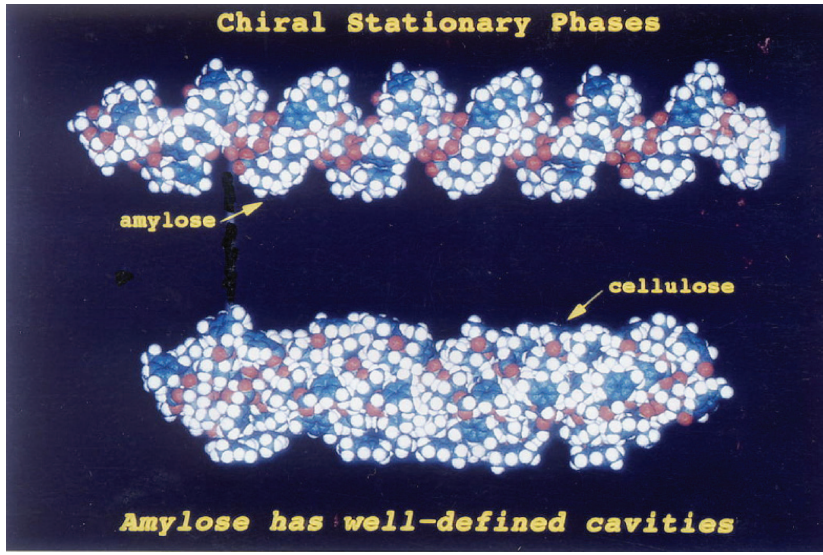


Figure 2. Three-dimensional structure of amylose and cellulose polymers.

and amylose were also synthesized and used for the enantiomeric resolution (6, 23).

STATUS OF COMMERCIAL POLYSACCHARIDE CSPS IN THE MARKET

Presently, amylose and cellulose derivatives in use are tris-benzoate, tris-(4-methyl benzoate, trisphenylcarbamate, *tris*-(3,5-dimethylphenylcarbamate, tris-(R)-1-phenylethylcarbamate, tris-(S)-1-methylphenylcarbamate etc. They have been commercialized by different names such as Chiralcel and Chiralpak for cellulose and amylose, respectively, by Daicel Chemical Industries, Tokyo, Japan. Recently, some other industries such as Kromasil, Macherey Nagel, Knauer and Sepaserve have also introduced some chiral columns. The chiral columns commercialized by these companies are in normal and reversed phases separately and respectively. The trade name of chiral columns of Kromasil are AmyCoat (tris-3,5-(dimethylphenyl)-carbamate-amylose) and CelluCoat (tris-3,5-(dimethylphenyl)-carbamate-cellulose) in normal phase and AmyCoat RP and CelluCoat RP in reversed phase respectively. The commercial CSPs supplied by Macherey Nagel are Nucleocel-Alpha, Nucleocel-Alpha-S, Nucleocel-Alpha-RP-S, Nucleocel-Delta, Nucleocel-Delta-S, Nucleocel-Delta-RP and Nucleocel-Delta-RP-S having tris-3,5-(dimethylphenyl)-carbamate derivatives of amylose in alpha and cellulose in delta configurations respectively. The RP represents reversed phase while S denotes small particle size (5 μm). On the other hand Knauer introduced Europak 01 amylose-*tris*-(3,5-dimethylphenylcarbamate) and Eurocel 01 cellulose-*tris*-(3,5-dimethylphenylcarbamate chiral pak columns respectively, which can be used in both normal and reversed phases respectively. To the best of our information Sepaserve has merged in Knauer and no more in the marketed under their names.

APPLICATIONS

As discussed above polysaccharide CSPs have gained a good reputation in the chiral world. They are very effective and capable to work under normal, reversed and prohibited organic mobile phase modes, and that is why they have wide range of applications. These CSPs are available as coated which can be used in normal and reversed phase modes but not on the same column. But, recently, immobilized CSPs have been develop, which are capable to work under prohibited organic mobile phase modes enhancing the range of enantiomeric recognition capabilities. Polysaccharides have been used very frequently in HPLC as CSPs along

with few reports as mobile phase additives (MPAs). However, the research papers are available on these chiral selectors in capillary-electrochromatography, sub- and supercritical fluid chromatography and thin layer chromatography. Breifly, the applications of these phases for enantiomeric resolution of pharmaceuticals and drugs are discussed in the following sections.

High Performance Liquid Chromatography

The utility of these cellulose and amylose derivatives have found broad applicability in both analytical and preparative applications and to a lesser extent as a mobile phase additive. The following covers these areas individually.

Analytical Separations

Analytical separation is the first step in sample recognition ranging from mg to nanolevels of concentration. As usual, chiral chromatography also starts with the analytical scale. Many publications have appeared in the literature in this area of chromatography and some important efforts are cited herein. Okamoto et al. (22, 24) examined the chiral recognition capacities of cellulose tribenzoate (CTB) derivatives. The effect of the substituents on the phenyl ring of cellulose tribenzoate (Chiralcel OB) has been studied. Furthermore, the same group (25, 26) described the chiral recognition abilities of a series of cellulose phenylcarbamate derivatives. It has been observed that an introduction of an electron donating group or an electron withdrawing halogen at 3- and/or 4- position improved resolution capacities. But the substituents at position 2- showed poor chiral resolution capacity. The derivatives with hetero atoms substituents, such as methoxy and nitro groups, showed poor chiral recognition (25). Racemic compounds interact with polar substituents of chiral glucose residue, and, hence, bulky alkoxy substituents like isopropoxy and isobutoxy improved resolving capacities (27). Phenylcarbamate derivatives having both an electron donating, methyl group, and withdrawing substituents (halogens) on the phenyl moieties were found to exhibit high enantio-separation for many racemates, for example, 3,4- or 3,5-chloro-methylphenylcarbamates of cellulose showed particularly high chiral recognition ability (28–30). Okamoto et al. (30, 31) improved the resolution power of amylose CSPs by introducing methyl or chloro groups on phenyl moieties. However, in contrast to cellulose derivatives, *tris*-(4-methylphenylcarbamate) (27) and *tris*-(5-chloro-2-methylphenylcarbamate) (32) of amylose showed a high chiral recognition.

The cellulose *tris*-(3,5-dimethylphenylcarbamate) (CDMPC) and amylose *tris*-(3,5-dimethylphenylcarbamate) (ADMPC) are two most important derivatives for chiral resolution of a variety of racemates (26, 33). A comparison between two phases (CDMPC and ADMPC) for enantioseparation of a series of amidotetralines (34) and chiral sulfoxide (35) was performed and a complementary chromatographic behavior was observed. *Meta*- and *para*- (fluoro and methyl groups) substituted cellulose derivatives showed higher resolving power than *ortho*- and *meta*- substituted derivatives. Contrarily, amylose derivatives with the substituents at *ortho*- position also showed high chiral separation in comparison to *meta*- and *para*- substituents derivatives. The elution order was not influenced by the change of the substituents in either cellulose or amylose derivatives (36). Chankvetadze et al. (32) described that *ortho*-substituted phenylcarbamate derivatives of amylose showed high chiral recognition abilities while cellulose phenylcarbamate derivatives with *ortho*- substituents have poor chiral resolving power. Okamoto et al. (37) observed that fluoro, chloro, bromo and iodo groups at the 4-position, on the phenyl ring, resulted into high chiral recognition than the corresponding cellulose derivatives. Luo et al. (38) studied the resolution of new antianginal drug ranolazine enantiomers with the help of cellulose *tris*-(3,5-dimethylphenylcarbamate) (CDMPC) chiral stationary phases (CSPs) under both normal and polar organic mobile phase modes. Belaz et al. (39) separated omeprazole, lansoprazole and rabeprazole by using polysaccharide chiral selectors. Stringham et al. (40) resolved enantiomers of amines on Chiralpak AD-H columns with acidic additives like ethanesulfonic acid (ESA), methanesulfonic acid (MSA); resulted in improved resolution with methanesulfonic acid as an acidic additive. Myrdal et al. (41) analyzed the chiral separation of lipoxygenase metabolites by using Chiralcel OD-RH column. Yu et al. (42) reported the enantiomeric separation of fluoxetine derivatives by using Chiralpak AD-RH, Chiralpak AD and Chiralcel OD columns. The effect of the mobile phase composition and column temperature on the enantioseparation was discussed. A tentative chiral recognition mechanism was also proposed by the authors.

Caccamese et al. (43) separated the enantiomers of an aromatic amine and four aminoalcohols i.e., *N*-benzyl-α-methyl-benzylamine, phenylalaninol, tryptophanol, 2-diphenylhydroxymethyl)pyrrolidine and isoproterenol on amylose *tris*-(3,5-dimethylphenylcarbamate) and cellulose *tris*-(3,5-dimethylphenilcarbamate) CSPs. The best separation was on amylose *tris*-(3,5-dimethylphenylcarbamate). Sztojkov-Ivanov et al. (44) studied chiral separation of 1-(aminoalkyl)-2-naphthol analogs on Chiralcel OD-H and Chiralcel OD-RH columns using *n*-hexane-2-propanol-diethylamine or phosphate buffer/organic modifier mobile phases. The best results were obtained on 3,5-dimethylphenyl

carbamoylated cellulose columns under both normal and reversed phase modes.

Zhao and Pritts (45) reported chiral separation of proline derivatives (Boc-proline, Boc-2-methylproline, Boc-2-methylproline benzyl ester and Boc-2-methyl-4-hydroxy-proline benzyl ester) on Chiralpak AD-H column. The effect of mobile phase composition and column temperature were studied and good resolution was achieved by using a mobile phase of hexane, ethanol and 0.1% TFA. As per the authors, resolution was changed dramatically for prolines containing carboxyl or hydroxy group by changing 1% of ethanol, which suggests dominant role of hydrogen bondings in chiral recognition. Contrarily, for prolines containing a benzyl ester instead of hydroxy group, resolution was little affected with the changes of ethanol percentage showing a different chiral recognition mechanism, which might be due to inclusion, steric effect, or possible π-π interactions. Khan et al. (46) studied the chiral separation of frovatriptan enantiomers in bulk drug and pharmaceutical formulations on amylose based chiral stationary phase and showed the effects of the organic modifiers *viz*. 2-propanol, ethanol and diethyl amine. Xu et al. (47) described the enantioseparation of 2-aryl-1,3-dicarbonyl analogues by amylose *tris*-(3,5-dimethylphenylcarbamate), amylose *tris*-(S)-1-phenylethylcarbamate), cellulose *tris*-(3,5-dimethylphenylcarbamate) and cellulose *tris*-(4-methylbenzoate) respectively in normal phase conditions. Batter result were obtained on amylose *tris*-(3,5-dimethylphenyl carbamate).

Some workers attempted to optimize the chiral separations by varying mobile phase composition, flow, pH of eluent, temperature etc. Lee et al. (48) resolved racemates of N-fluorenylmethoxycarbonyl α-amino acids (N-FMOC) on cellulose *tris*-(3,5-dimethylphenylcarbamate) (Chiralcel OD), amylose *tris*-(3,5-dimethyl-phenylcarbamate) (Chiralpak AD) and cellulose *tris*-(4-methylbenzoate) (Chiralcel OJ) columns. The influence of acetonitrile composition and pH of the mobile phase was studied and the best separation was with 40% acetonitrile in 50 mM phosphate buffer (pH 2). However, increasing the composition of acetonitrile to 50% on Chiralcel OD yielded a considerable decrease of retention time with minimum loss of resolution.

Ye et al. (49) studied the effect of acidic and basic additives on the enantio-separation of basic drugs using polysaccharide-based chiral stationary phases. The different commercially available CSPs i.e., AD, AS, OD, OJ, OG, OB, and OC were tested for the enantiomeric resolution of nine commercially available β-blockers i.e., alprenolol, atenolol, metaproterenol, metoprolol, clenbuterol, terbutaline, propranolol, oxprenolol and pindolol. The significantly improved selectivities were obtained for basic probe drugs with the acidic additive [(ethanesulfonic acid (ESA)] than the basic additive [butylamine, (BA)]. The best results were obtained with Chiralpak AS and ethanesulfonic acid. As per

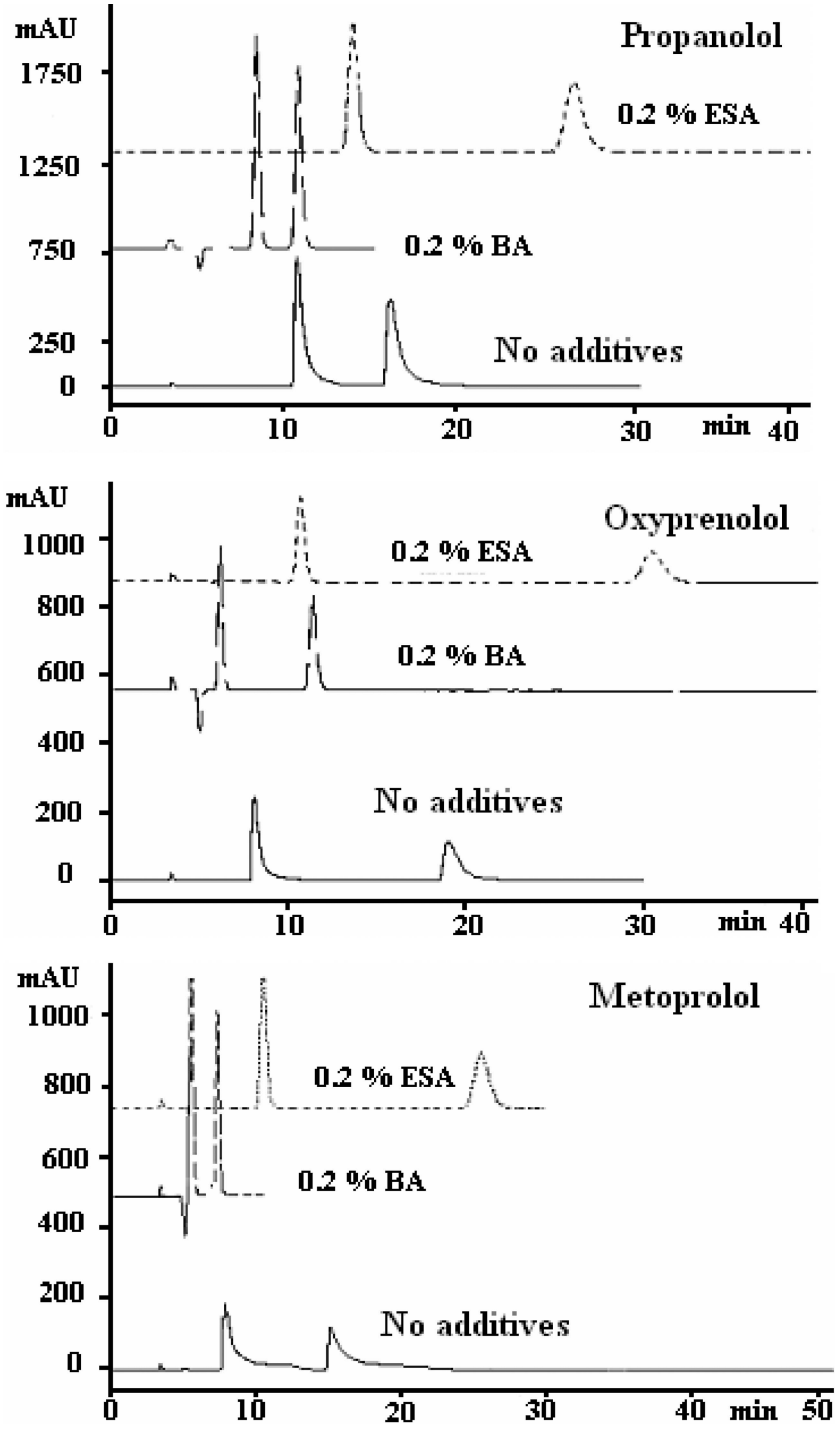
the authors the beneficial effects of acidic additive in enantio-separations could significantly improve the applicability of polysaccharide-based CSPs for the enantio-separation of basic analytes. Figure 3 shows the effect of several of ESAs and BAs on chiral resolution of propranolol, oxyprenolol and metoprolol, which clearly indicate dominant effects of these additives. Similarly, Bielejewska et al. (50) described the influence of the mobile phase composition on chiral separation of 15 pyrrolidin-2-ones by using polysaccharide CSPs (Chiralpak AD, Chiralpak IA and Chiralcel OD). The optimization of resolution was achieved by using ethanol or 2-propanol as mobile phase modifiers. Amylose columns exhibited better enantioselectivity than cellulose ones as all racemates separated on a Chiralpak IA and Chiralpak AD columns.

Rao et al. (51) validated a HPLC method for chiral resolution of bicalutamide using amylose *tris*-(3,5-dimethylphenylcarbamate) as a chiral stationary phase. The baseline separation was achieved within 10 min on Chiralpak AD-H column using *n*-hexane-2-propanol (65:35 v/v) as mobile phase at a flow rate of 1.0 mL/min. The effects of 2-propanol, ethanol and temperature on were studied and the method was validated in terms of accuracy, precision and linearity. Furthermore the same authors (52) described enantiomeric resolution of doxazosin mesylate and its process related substances, on Chiralpak AD-H and Chiralcel OD-H columns. The effect of alcoholic modifiers on the resolution was studied and a good separation was achieved by using 2-propanol (Figure 4). The effects of structural features of the solutes and solvents on discrimination between the enantiomers were also described.

Myrdal et al. (41) studied the effect of temperature on chiral resolution of lipoxygenase metabolites. Figure 5 indicates the effect of temperature on chiral resolution of 13-hydroxyoctadecadienoic acid at 0 and 35°C. And it is clear from this Figure that this racemates is partially resolved at 35 while it is base line separated at zero degree centigrade temperature. Some other applications of these CSPs at analytical scale are summarized in Table 1.

Preparative Separations

In addition to analytical scale, polysaccharide CSPs have also been used for the resolution of enantiomers at preparative scales; cellulose triacetate has good loading capacity and used at industrial scale (53, 54). The cellulose triacetate (CTA) CSPs have been used for the resolution of aliphatic aromatic compounds at a preparative scale (55–58). Along with experimental conditions, molecular weight of cellulose also effects the chiral separation (59, 60). Francotte et al. (56, 58, 61, 62) resolved some drugs on CTB derivatives in large quantities. Cirilli et al. (63) also separated the imidazole derivatives by HPLC at semi-preparative scale. Luo et al. (38)



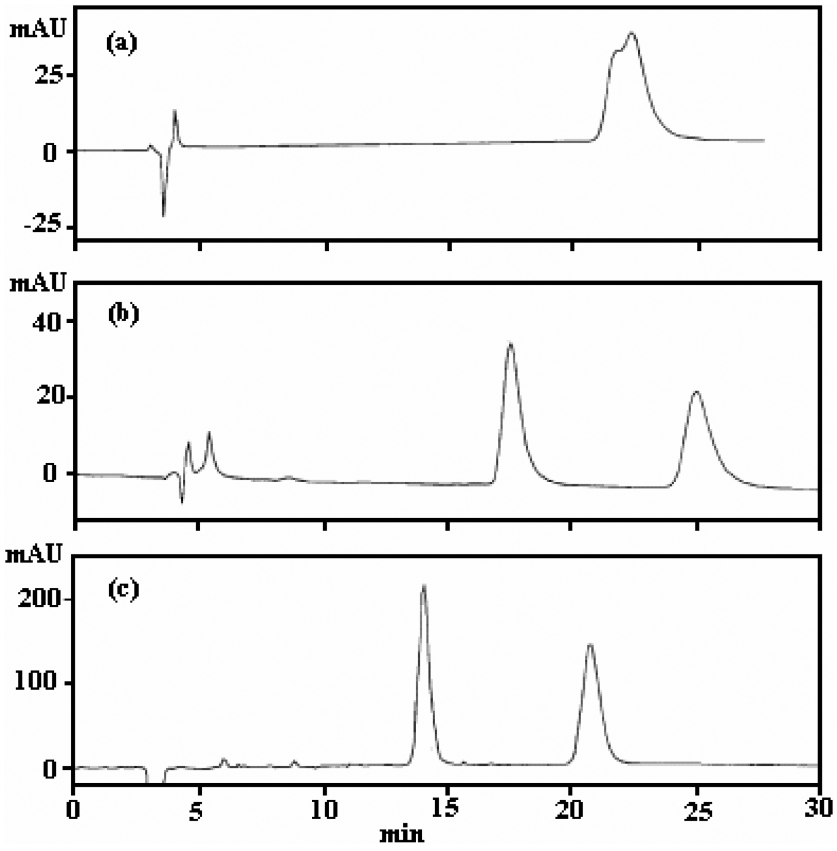


Figure 4. The effect of the modifier on chiral separation of doxazosin mesylate, (a) ethanol (35%), (b) 1-propanol (20%) and (c) 2-propanol (30%) on Chiralpak AD-H column (52).

described the chiral resolution of new antianginal drug ranolazine enantiomers at semi-preparative scale and good separation was achieved by using cellulose *tris*-(3,5-dimethylphenylcarbamate) (CDMPC) chiral stationary phases under both normal and polar organic modes.

Jansen et al. (64) reported semi-preparative enantiomeric separation of a series of putative melatonin receptor agents using *tri*-acetylcellulose as chiral stationary phase and observed that first eluting enantiomer was around 99% pure. Magri et al. (65) reported semi-preparative chiral separations of some novel atropisomeric quaternary

Figure 3. The chromatograms of β-blockers showing the effect of mobile phase additives on Chiralpak AS column by using ethanol-hexane (10:90, v/v) as mobile phase (49).

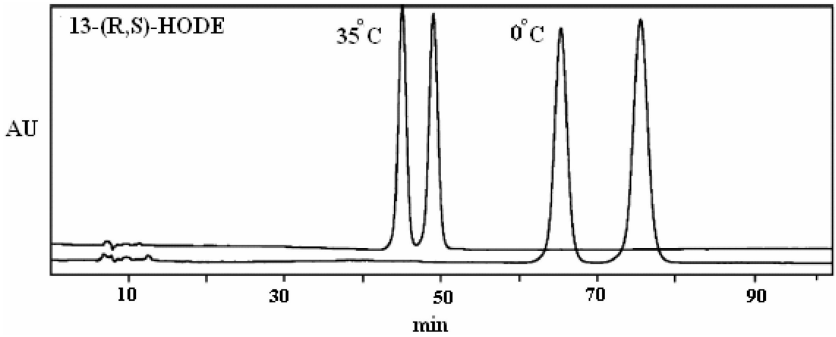


Figure 5. The effect of temperature on chiral resolution of 13-hydroxyoctadecadienoic acid at 0 and 35 °C. Column: Chiralcel OD-RH, mobile phase: methanol-5 mM TFA-acetonitrile (10:41:49, v/v) with 0.25 mL/min. flow rate (41).

and ternary 1,2-disubstituted 1,4,5,6-tetrahydropyrimidinium salts. The authors compared the experimental data in order to establish the factors influencing the magnitude of the barriers and with those corresponding to the parent amidines. The chiral columns used OD-R, OJ-R, AD-RH with mobile phases of acetonitrile and water in different combinations. de Veredas et al. (66) reported a simulated moving bed chromatographic chiral separation of a baclofen precursor (N-Boc-4-[*p*-chloro-phenyl]-2-pyrrolidone) by using polysaccharide carbamate as chiral stationary phase (cellulose *tris*-(3,5-dimethylphenylcarbamate) at semi-preparative scale. The method was capable of providing high purity enantiomers of 1.0 g/day. Collina et al. (67) reported semi-preparative scale resolution of *N,N*-dimethyl-3-(naphthalen-2-yl)-butan-1-amines on Chiralcel OD column.

In addition to the coated CSPs, immobilized chiral phases have been used for semi-preparative separations in liquid chromatography. Cirilli et al. (68) described semi-preparative chiral separations of mianserin and a series of aptazepine derivatives on immobilized polysaccharide based chiral stationary phases (Chiralpak IA). The non-conventional dichloromethane based eluents have expanded the chiral resolving ability of the immobilized Chiralpak IA to perform mg-scale enantioseparations with an analytical size column. The authors assigned absolute configuration of the separated enantiomers by comparing their chiroptical data with those of structurally related mianserin. Furthermore, the same authors (69) reported semi-preparative chiral resolution of 3,4-dihydropyrimidin-4(3H)-one derivatives (with antiviral, antiproliferative and morphological differentiation activities against melanoma cells) on Chiralpak IA column. The non-standard solvents such as ethyl acetate, methyl tertbutyl ether, or dichloromethane were used. The authors reported mg-scale separations and used further for chiroptical properties.

Table 1. Chiral separations of racemates on polysaccharide CSPs in different modalities of liquid chromatography

Racemates	Mobile Phases	CSPs	Refs.
Chiral Columns of Diacel Chemical Company, Japan			
Analytical Scale HPLC Separation on Coated CSPs			
Metoprolol, Tolamolol, Nebivolol Econazole, Cromakalim Etodolac	2-Propanol	*tris*-(3,5-dichlorophenyl-carbamate)	(162)
Metipranolol	*n*-Hexane-Propan-2-ol-diethylamine	Chiralcel OD	(163)
Timolol	*n*-Hexane-2-Propanol	Chiralcel OD	(164)
Alprenolol, Atenolol, Bisoprolol, Bupranolol, Carazolol, Cartelol, Mepindolol,Metoprilol, Nadolol, Oxprenolol, Tertatolol, Tolamolol Pindolol, Propranolol,	*n*-Hexane-2-Propanol-Diethyl-amine / Perchlorate Solution-Acetonitrile	Chiralcel OD/Chiralcel OD-RH	(165)
Ketoprofen	Acetonitrile -0.02 M Perchlorate Buffer (pH 2.0)-Methanol	Chiralcel OJ-R	(148)
Ibuprofen esters	*n*-Hexane	Chiralcel OJ	(166)
Flurbiprofen	Water-Acetonitrile	Chiralpak AD-RH	(167)
Doxazosin mesylate	*n*-Hexane-Alcohol -0.1% Diethylamine	Chiralpak AD-H	(149)
Methylphenidate	Hexane-Ethanol-Methanol: TFA	Chiralpak AD Chiralcel OD,OJ,OC,OB	(133)
Fipronil	*n*-Hexane-Iso-butanol	Cellulose-tri (3,5-dimethylphenylcarbamate)	(168)
Cromakalim	Water-Acetonitrile	Chiralpak AD-R, Chiralcel OD-R, Chiralcel OJ-R	(149)
Tamsulosin	50 mMKPF6-Acetonitrile	Chiralcel OD-RH	(169)

(*continued*)

Table 1. Continued

Racemates	Mobile Phases	CSPs	Refs.
Apomorphine	Acetonitrile-0.05 M Sodium-perchlorate	Chiralcel OD-R	(170)
Cizolirtine, cizolirtine-*N*-oxide, *N*-desmethyl-cizolirtine, 5(a-hydroxy-benzyl)-1-methyl pyrazole	*n*-Hexane- 2-Propanol-Triethylamine	Chiralpak AD	(171)
Benzoxazolinone	*n*-Hexane-Alcohol	Chiralcel OD-H	(172)
Ondansetron	*n*-Hexane- 95% Ethanol-2-propanol-Acetonitrile	Chiralcel OD	(173)
Pyridazinone derivatives	*n*-Hexane-Ethanol-2-Propanol	Chiralcel OJ	(174)
Tetralone derivative	Acetonitrile-Water-Triethylamine	Chiralpak AD-RH	(175)
Levetiracetam	Hexane-Isopropanol	Chiralpak AD-H	(176)
β-Lactam	Water-Acetonitrile	Chiralcel OD-RH	(177)
Vesamicol and benzovesamicol-analogues	*n*-Hexane-2-Propanol-Diethylamine	Cellulose *tris*-(3,5-di-methylphenyl carbamate)	(178)
2-Aryl-1,3-dicarbonyl-analogues	*n*-Hexane-Isopropyl alcohol	Chiralpak AD-H	(47)
1-[(benzofuran-2-yl)-5-nitrophenyl methyl]-Tetrazole	*n*-Hexane-2-Propanol	Chiralcel OD-RH	(179)
1-[(benzofuran-2-yl)-5-bromophenyl methyl] - tetrazole	Water-Acetonitrile	Chiralcel OJ-R	(179)
Triazole and Tetrazole-derivative	2-Propanol-Acetonitrile	Chiralpak AD-RH	(180)
Boc-proline	Hexane-Ethanol-0.1% TFA	Chiralpak AD-H	(45)
Bicalutamide	*n*-Hexane-2-propanol	Chiralpak AD-H	(51)
Armodafinil	*n*-Hexane-Ethanol- TFA	Chiralcel OD-H	(181)
Torcetrapib (TTB)	*n*-Hexane-Isopropyl alcohol	Chiralpak AD-H	(182)
N-benzyl-α-Methyl-benzylamine	*n*-Hexane-2-Propanol- TFA	Amylose *tris*-(3,5-dimethyl-phenyl carbamate)	(43)

Kynurenine (KYN)	Water-acetonitrile-methanol-0.1% acetic acid	Chiralcel OJ-RH	(183)
Mineralocorticoid receptor (hMR) antagonist	Alcohol-Acetonitrile	Chiralcel OJ-H	(184)
Bnzoxathiepin derivative	Methanol-Ethanol-Diethylamine	Chiralcel OJ-H	(185)
1,4-Disubstituted-piperazines	5% of 2-Propanol in Hexane	Cellulose *tris*-(4-methylbenzoate)	(186)
trans-Kielcorin C phenylcarbamate	Alcohol-Hexane	*Tris*-3,5-dimethyl-	(187)
Pyridoglutehimide	Acetonitrile-0.3 M Aq. sodium perchlorate	Chiralcel OD-R	(188)
Thio-glycidyl ethers	Hexane-2-Propanol	Amylose-*tris*-(phenylcarbamate)	(189)
Biphenyl compounds	Hexane-Ethanol	Amylose *tris*-(3,5-dimethyl-phenylcarbamate)	(190)
Cannabinoids	Ethanol-*n*-Hexane	Chiralpak AD	(191)
Preparative Scale HPLC Separation on Coated CSPs			
Naringenin	*n*-Hexane-Alcohol	Chiralcel OD-H, Chiralpak AS-H	(192)
Albendazole-	*n*-Hexane- Alcohol sulfoxide	amylose *tris* (3,5-dimethyl-phenylcarbamate)	(193)
Linezolid	Hexane- 2-Propanol-TFA	Chiralpak AD	(194)
Preparative Scale HPLC Separation on Immobilized CSPs			
Mianserin & aptazepine derivatives	Dichloromethane	Chiralpak IA	(68)
3,4-dihydropyrimidin-4(3H)-one derivatives	Ethyl acetate- Methyl tert butyl ether- Dichloromethane	Chiralpak IA	(69)
Analytical Scale Capillary Electro-chromatography Separation on Coated CSPs			
β-Blockers, diuretics & benzodiazepines	Hexane-Dioxane-2-Propanol	Chiralcel OD	(75)
Thalidomide & metabolites	2.5 mM Ammon. acetate	Chiralpak AD	(78)
Piprozolin, indapamide, glutethimides & *trans*-stilbene	2.5-10 mM Ammon. acetate	Chiralpak AD, Chiralcel OD & Chiralcel OJ	(79, 195, 196)

(*continued*)

Table 1. Continued

Racemates	Mobile Phases	CSPs	Refs.
Ambucetamide, benzyl-2-(benzylsulfinyl)benzoate, etozolin, norgestrol, omperazole, piprozolin & thalidomide	15 mM Ammon. acetate	Chiralcel OD	(197)
Benzyl-2-(benzyl-sulfinyl) benzoate 2-(benzylsulfinyl) benzamide, piprozolin & etozolin	2.5 mM Ammon. acetate	Chiralcel OD	(76–78)
Warfarin & praziquantel	5 mM Acetic acid-TEA	Cellulose 2,3-O,O-bis(phenylcarbamate)	(198)
Tröger's base, benzoin, praziquantel, *& trans*-stilbene	14.2 mM Acetic acid-DEA	Cellulose 2,3-O,O-bis(phenylcarbamate)	(199, 200)
Thalidomide	–	Chiralcel OJ	(78)
Analytical Scale Sub-Critical Fluid Chromatography on Separation Coated CSPs			
Acidic drugs	CO_2-Alcohol	Chiralpak AD	(96)
Alkylalkanols	CO_2– Methanol-TFAA-TEA	Chiralcel OB, Chiralcel OD	(201)
Basic racemates	Ethanol-ESA	Chiralpak AD-H	(95)
Benzodiazepines	CO_2-Methanol-TFAA-TEA	Chiralcel OD-H, Chiralpak AD	(202) (203)
Bezothiazepines	CO_2-DEA	Chiralcel OD	(204)
Calcium channel blockers	CO_2-Methanol-TFAA-TEA	Chiralcel OD	(201)
β-Blockers	CO_2-Methanol-TFAA-TEA	Chiralpak AD	(202)
Imidazole derivatives	CO_2-Methanol-TFAA-TEA	Chiralcel OJ, Chiralpak AD, Chiralpak AS	(201)
N-Protected amino acids/esters	CO_2-Methanol-TFAA-TEA	Chiralpak AD	(201)
Barbiturates	CO_2-Methanol-TFAA-TEA	Chiralcel OJ	(201)
β-Andrenoreceptor blocking agent	CO_2-Methanol-TFAA-TEA	Chiralcel OD	(201)
Triazole pesticides	Alcohol-TFAA-TEA	Chiralpak AD	(98)
β-Blockers		AmyCoat	(104)

		CelluCoat	(104)
Analytical Scale HPLC Separation on Immobilized CSPs			
Cyclopropen	*n*-Hexane-2-propanol	Chiralpak IA	(122)
Bupivacaine	Acetonitrile-DEA	Chiralpak IA	(8)
Hexobarbital Methaqualone Metalaxyl Bupivacaine Ketamine Terfenadine	MtBE	Chiralpak IA	(8)
Lorazepam Disopyramide Indapamide	MtBE-Ethanol	Chiralpak IA	(8)
Oxazepam	MtBE -Acetone	Chiralpak IA	(8)
Thalidomide	MtBe-1,4-Dioxane	Chiralpak IA	(8)
Alprenolol Chlophedanol Chlopheniramine Promethazine Diperodon Propafenone	*n*-Hexane –THF-DEA	Chiralpak IA	(8)
Glutethimide Methaqualone	Ethanol-THF	Chiralpak IA	(8)
Temazepam	*n*-Hexane -THF	Chiralpak IA	(8)
N-alkylated barbiturates and analogs of thalidomide	*n*-Hexane-2-propanol	Chiralpak IB	(124)
Tris(2-phenylpyridine) iridium (III)	Hexane-methyl chloride-Dichloromethane	Chiralpak IA	(120)
N-Alkylated barbiturates &3-alkylated analogs of thalidomide	*n*-Hexane-2-propanol	Chiralpak IA	(123)
15 Pyrrolidin-2-ones	Ethanol	Chiralpak IA	(50)
Piperidine-2,6-dione	Methyl-tert-butyl ether-THF	Chiralpak IA, Chiralpak IB	(205)
Analytical Scale HPLC Separation on Coated CSPs (Xenobiotics)			
Hexconazole, Tebuconazole	*n*-Hexane-Isopropanol	Amylopectin-*tris*-(phenylcarbamate)	(206)

(*continued*)

Table 1. Continued

Racemates	Mobile Phases	CSPs	Refs.
Tebuconazole	*n*-Hexane-EtOH	Cellulose *tris*-(3,5-dimethylphenyl carbamate)	(207)
Econazole, Miconazole, Sulconazole	*n*-Hexane-2-Propanol-Diethyl-amine	Chiralpak WH	(208)
Econazole, Miconazole, Sulconazole	*n*-Hexane-2-Propanol-Diethyl-amine	Chiralcel OD, OJ, OB, OK, OC and OF	(134)
Chiral Pesticides	*n*-Hexane-Isopropanol	Amylose *tris*-(S)-1-phenylethylcarbamate	(209)
Trichloronate	*n*-Hexane-*n*-Heptane-Ethanol	Chiralcel OJ	(210)
Trans-chlordane, *cis*-chlordane, heptachlor	*n*-Hexane	Chiralcel OD	(211)
α-Hexachloro-Cyclohexane	*n*-Hexane-2-Propanol	Chiraacerl OJ	(211)
Imazethapyr, Imazaquin, and Imazamox Imazapyr, Imazapic,	50 mM Phosphate buffer-Acetonitrile	Chiralcel OD-R	(212)
Imazethapyr, Imazamox and Imazaquin	*n*-Hexane-(0.1% TFA)-Alcohol	Chiralcel OJ	(212)
Chiral Columns of Kromasil, Sweden			
Analytical Scale by HPLC Separation on Coated CSPs			
Alprenolol Atenolol Atropine Hydroxyzine Propanolol	Heptane-Ethanol-DEA	CelluCoat	(104)
Ambucetamide Ketamine Oxamniquine Oxazepam Oxprenolol 1-phenylethylamine Troger's Base	Heptane-2-propanol-DEA	CelluCoat	(104)
CBZ Alanine Ibuprofen Naproxen Proglumide	Heptane-2-propanol-TFA	CelluCoat	(104)
Benzoine Binaphthol Carbinoxamine Trans-Stilbene oxide Trifluoro-anthrylethanol	Heptane-2-propanol	CelluCoat,	(104)
Mianserin	Methanol-DEA	CelluCoat,	(104)

Ambucetamide Carbinoxamine Oxamniquine Oxprenolol Troger's Base Verapamil	Heptane- 2-propanol-DEA	AmyCoat	(104)
Benzoine Bcetin Hexobarbital Trans-Stilbene oxide Trifluoro-anthrylethanol	Heptane-2-propanol	AmyCoat	(104)
Binaphthol CBZ Alanine Ketoprofen Naproxen Proglumide	Heptane-2-propanol - TFA	AmyCoat	(104)
Alprenolol	Heptane-Ethanol-DEA	AmyCoat	(104)
Metoprolol Mianserin Propafenone Propanolol	Methanol-DEA	AmyCoat	(104)
Thalidomide	Methanol	AmyCoat	(104)
Indapamide 4-phenyl-2butanol Pindolol Warfarin	Acetonitrile-water	CelluCoat RP	(104)
Flurbiprofen 2-Methyl-1-tetralone Warfarin	Acetonitrile-water	AmyCoat RP	(104)
Ibuprofen	Methanol-water-acetic acid	AmyCoat RP	(104)
Chiral Columns of Macherey Nagel, Germany			
Analytical Scale HPLC Separation on Coated CSPs			
Trans-stilben oxide	*n*-Hexane-2-Propanol	Nucleocel-δ	(213)
Metoprolol	*n* -Heptane-2-propanol-DEA	Nucleocel-δ	(213)
1-(1-naphthyl)ethanol Flavanone	*n* -Heptane-2-propanol	Nucleocel-δ	(213)
Naproxen Ketoprofen	*n*-Hexane-2-Propanol-TFA	Nucleocel-α S	(213)
Cannabidiol	*n* -Hexane-ethanol	Nucleocel-α S	(213)
Hexobarbital Fenoxaprop-ethyl *Trans*-stilben oxide	*n* -Heptane-isopropanol	Nucleocel-α S	(213)
Troeger's base	*n* -Hexane-isopropanol	Nucleocel-α S	(213)
Benzoine Chlorpheniramine	*n* -Hexane-isopropanol-DEA	Nucleocel-α S	(213)
Verapamil	*n* -Heptane-2-propanol/DEA	Nucleocel-α S	(213)

(*continued*)

Table 1. Continued

Racemates	Mobile Phases	CSPs	Refs.
Thalidomide	Methanol	Nucleocel-α S	(213)
Indapamide	Acetonitrile-water	Nucleocel-δ –RP	(213)
Wafarin	Acetonitrile-1% H_3PO_4, pH2	Nucleocel-α -RP S	(213)
Linalool	Acetonitrile-water	Nucleocel-α -RP S	(213)
Chiral Columns of Knauer, Germany			
Analytical Scale HPLC Separation on Coated CSPs			
Etozoline	Methanol	Eurocel 01	(214)
Flavonone	*n*-Heptane-isopropanol	Eurocel 01	(214)
Pindolol	20 mM sodium borate buffer pH 9	Eurocel 01	(214)
Alpha-tocopherol	Heptane-butanol	Europak 01	(214)
Trans-stilbene oxide	Hexane-2-propanol	Europak 01	(214)
Analytical Scale Thin Layer Chromatography Separation on Coated CSPs			
Tröger's base	—	Cellulose acetate	(55)
DL-Tryptophan & derivatives	—	Microcrystalline cellulose	(109–113)
β-blockers	—	Cellulose phenyl carbamate	(114)
Amino acids	—	Chitin and chitosan	(116)

Besides, above cited modalities, Subcritical fluid chromatography (SFC) has also been used for semi-preparative chiral separations of a few racemates. The work reported by some workers is discussed herein. Saito et al. (70) separated the enantiomers of DL-flavanone at a preparative scale by using Chiralcel OD column. Oka and coworkers (71) resolved four optical isomers of antidiabetic drug troglitazone on cellulose CSPs by preparative SFC. Recently, Toribio et al. (72) separated enantiomers of omeprazole at semi-preparative scale by supercritical fluid chromatography (SFC) on Chiralpak AD column. The authors studied the effect of two organic modifiers (ethanol and 2-propanol), different injection volumes and concentrations of omeprazole; in order to obtain high enantiomeric purities and production rates. As a result of exhaustive optimization better results were achieved by using concentration overloading instead of volume overloading. The chiral preparative separations of some racemic compounds are summarized in Table 1.

Capillary Electro-Chromatography

Capillary electro-chromatography (CEC) works on the combined principles of liquid chromatography and capillary electrophoresis. Therefore, it is a good technique for the chiral separation of enantiomers by using polysaccharides as chiral selectors. CSPs in this modality of chromatography are not much developed and most of the work is related to MPAS. However, few reports are available on chiral separations by using this technique involving polysaccharides CSPs. Wistuba and Schuring (73) and Lämmerhofer (74) reviewed the chiral separations in CEC by using polysaccharide chiral selectors. These authors described the strategies, concepts and column technologies that have been utilized to succeed in highly efficient enantiomer separations by non-aqueous CEC. Enantiomeric resolutions in CEC have been carried out by using packed capillaries with polysaccharides chiral selectors (75–78), which were fabricated by slurry packing method (77, 78).

Chankvetadze et al. (76, 78) has carried out the chiral separation of different racemates by using CEC; high resolving power of Chiralpak AD [amylose *tris*-(3,5-dimethylphenylcarbamate) coated on wide pore of aminopropylsilanized silica gel] in comparison to Chiralcel OD and Chiralcel OJ [cellulose *tris*-(3,5-dimethylphenylcarbamate) and cellulose *tris*-(4-methylbenzoate)] CSPs for thalidomide. Enantioseparations of β-blockers, benzodiazepines and diuretics were performed in fused silica capillaries packed with silica gel, which was modified by coating with cellulose *tris*-(3,5-dimethylphenylcarbamate) (75). Furthermore, Chankvetadze et al. (76) studied the effect of amount of *tris*-(3,5-dimethylphenylcarbamate) loaded on silica gel on chiral resolution of

2-(benzylsulfinyl)benzamide, which is shown in Figure 6. It was observed that 4.8% (w/w) amount has resulted in the best resolution. Besides, Chankvetadze et al. (77) reported the effect of pore size of silica gel and concentration of buffer on the chiral resolution of piprozolin and concluded that the ionic strength of a buffer solution dramatically affected the electrosomotic flow generation and intraparticle perfusive flow especially for silica gel of pore size below 12 nm.

Girod et al. (79) studied the chiral resolution of some racemates in non-aqueous capillary CEC with cellulose and amylose *tris*-(3,5-dimethylphenylcarbamates) (Chiralcel OD and Chiralpak AD) respectively. Francotte et al. (80) studied the chiral resolution of benzoin,

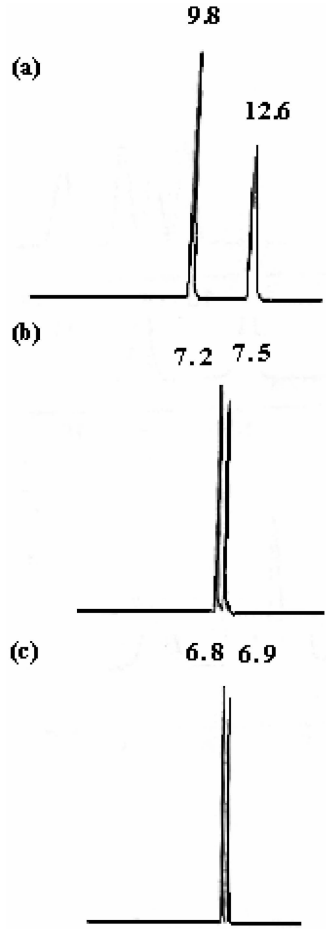


Figure 6. The effect of amount of *tris*-(3,5-dimethylphenylcarbamate) loaded on silica gel on chiral resolution of 2-(benzylsulfinyl)benzamide (76).

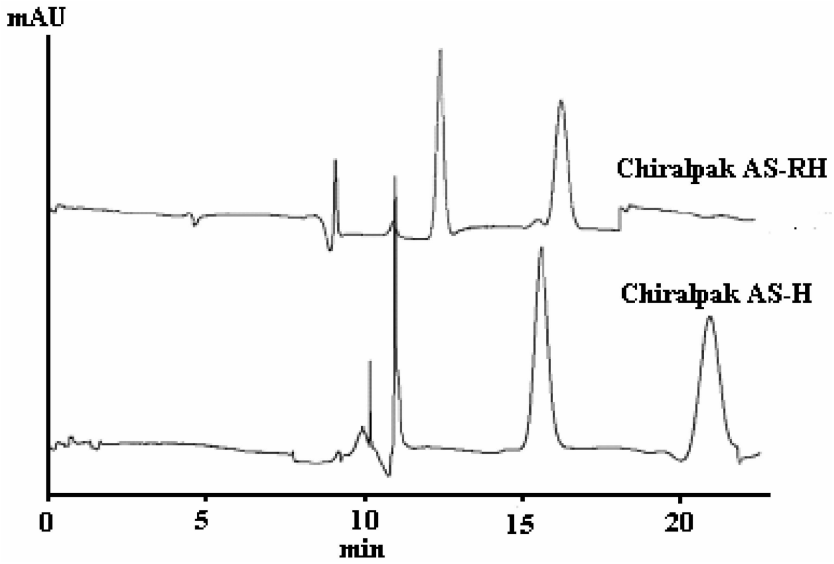


Figure 7. A comparison between Chiralpak AS-RH and AS-H for the separation of warfarin (82).

indapamide, glutethimide, lormetazepam, α-1-hydroxyethylnaphthalene enantiomers by using packed CEC. Mangelings et al. (81–83) carried out remarkable work on the optimization of the chiral separations in CEC by using a variety of racemates (alprenolol, metoprolol, acebutolol, oxprenolol, pindolol, propranolol, mianserin, tetramisole, oxazepam). Furthermore, the same authors (82) described the influence of normal and reversed phase use on chiral separations for two basic (pindolol, tetramisole), two acidic (acenocoumarol, warfarin), one bifunctional (oxazepam) and one neutral (praziquante) compounds by using Chiralcel OD, Chiralcel OJ, Chiralpak AD and Chiralpak AS columns (Figure 7). The chiral separations on CEC by using polysaccharide chiral phases are summarized in Table 1.

Sub- and Super Critical Fluid Chromatography

Sub- and super critical fluid chromatographic modalities have some advantages in chiral separations due to critical temperature and pressure of mobile phases used. Polysaccharide CSPs have been tested for enantiomeric resolution in these modalities of liquid chromatographies (84). Enantiomers of β-blockers have been resolved on cellulose *tris*-(3,5-dimethylphenylcarbamate) CSPs using these modalities of liquid chromatography (85, 86). Bargmann-Leyder et al. (87) also reported chiral

separations of β-blockers and other drugs enantiomers on Chiralcel OD and Chiralpak AD columns and studied the effects of pressure on the chiral resolution of β-blockers by using Chiralpak AD, while no pressure effect was observed on Chiralcel OD. Furthermore, these authors studied a comparison of the chiral separations of β-blockers on HPLC and SFC; with good separation in SFC in comparison to HPLC. Overbeke et al. (88) resolved benzoxaprofen, temazepam and mephobarbital on Chiralcel OJ. The effect of enantioselectivity of carbon dioxide on acidic drugs (benzoxaprofen, temazepam and mephobarbital), profen and barbiturate derivatives was carried out on Chiralcel OJ using acetonitrile or methanol as organic modifiers.

Phinney et al. (89) reported chiral resolution of a series of benzodizepines. Wang et al. (90) applied Chiralcel OD for the enantiomeric resolution of camazepam and its metabolites. Siret et al. (91) reported chiral resolution of calcium channel blockers on Chiralcel OJ. Kot et al. and Wilson (92, 93) used amylose CSPs for the resolution of non-steroidal inflammatory drugs (ibuprofen, flurbiprofen and related drugs). Stringham et al. (94) resolved the enantiomers of four intermediates encountered in synthetic process development for antiviral drugs on Chiralcel OD. The same authors (95) reported chiral separation of basic compounds by SFC using Chiralpak AD-H. According to the authors, an incorporation of ethanesulfonic acid into sample solution and mobile phase resulted into a dramatic improvement in the separations; as 36 of 45 basic compounds separated successfully. Gyllennhaal and Stefansson (96) reported chiral separations of four 2-substituted propionic acid drugs on Chiralpak AD column. Blackwell (97) reported the enantiomeric resolution of isoxazoline-based IIb/IIIb receptor antagonists on Chiralcel OD-H column using various mobile phase additives.

Toribio et al. (98) carried out chiral separations of propiconazole pesticide on Chiralpak AD (Figure 8). Toribio et al. (99) reported the chiral separation of ketoconazole and its precursors on Chiralpak AD and Chiralcel OD. The authors reported that alcohol modifiers provided better enantioselectivity than acetonitrile (Figure 9). Bernal et al. (100) described the chiral separation of four 1,3-dioxolane derivatives on an amylose based column by optimizing temperature and pressure effects. Optimization is a time consuming process and, hence, automated column and modifier selection valves may be useful to carry out the chiral separations of a variety of racemates by using sub-SFC/SFC (101). Zhao et al. (102) studied the chiral separation of selected proline derivatives on polysaccharide CSP; and the results were compared with HPLC indicating better separations in SFC. Ottiger et al. (103) carried out the enantioseparation of 1-phenyl-1-propanol on Chiralcel-OD in super-critical fluid chromatography with good resolution factors. Recently, Kromasil (104) introduced AmyCoat and CelluoCoat columns for use in

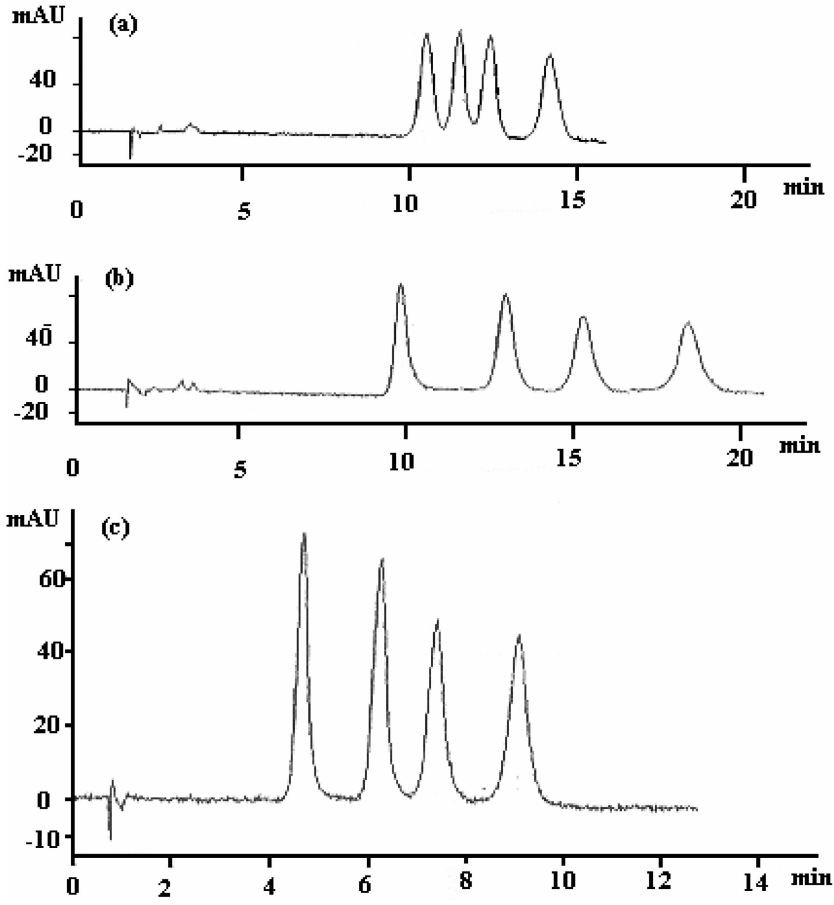


Figure 8. Chromatograms of enantiomeric resolution of propiconazole in (a) 3% (v/v) ethanol 2 mL/min, (b) 5% (v/v) 2-propanol at 2 mL/min and (c) 5% (v/v) 2-propanol at 4 mL/min. on Chiralpak AD (98).

normal and reversed phase modes, for chiral separation of β-blockers, profens and other chiral drugs in SFC. It has been observed that the peaks were sharp and base line separation was achieved. The results indicate a successful application of these phases. The enantiomeric resolutions on SFC using polysaccharides CSPs and are given in Table 1.

Thin Layer Chromatography

Classical thin layer chromatography (TLC) has been used for chiral separations first of all by Hesse and Hagel (55) to separate the Tröger's base

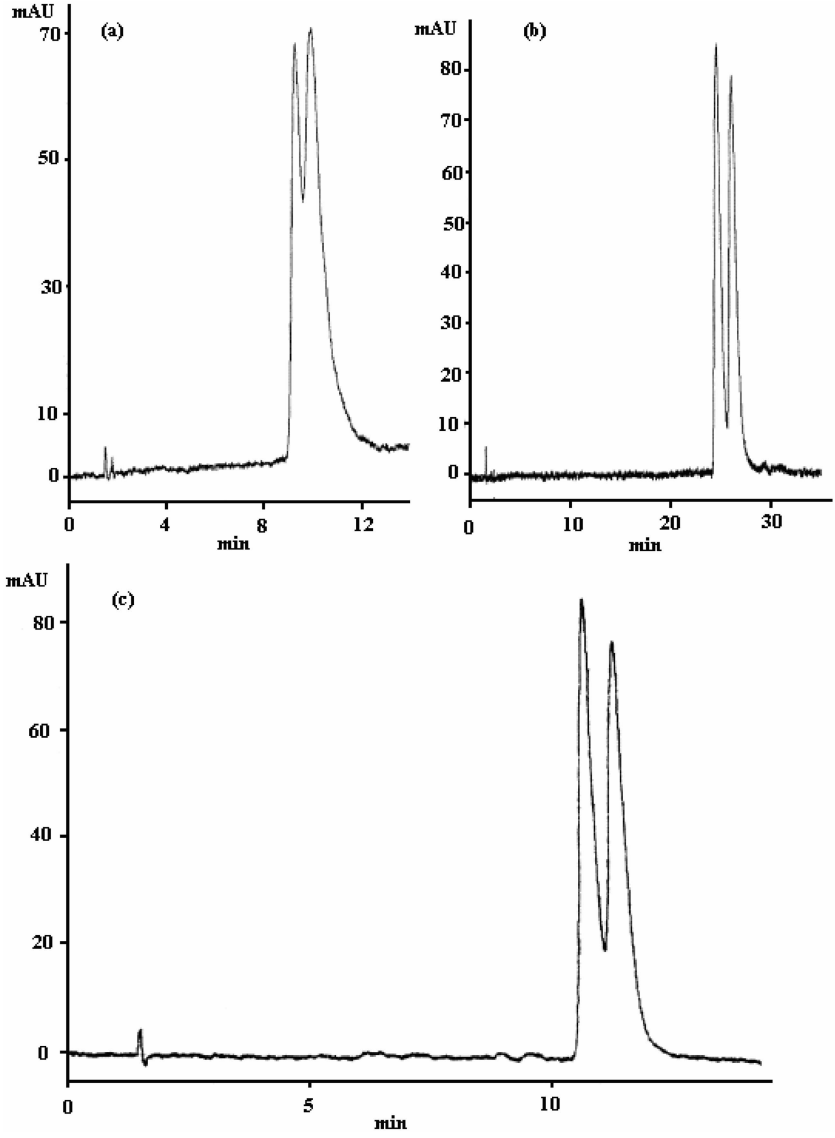


Figure 9. The chiral chromatograms of cis-2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)1,3-dioxolane-4-methanol (1) and cis-[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)1,3-dioxolane-4-yl] methyl p-toluensulfonate (2) with (a) compound 1 on Chiralpak AD column, 10% methanol, (b) compound 1, Chiralcel OD column, 5% methanol and (c) compound 2 Chiralpak OD column, 15% ethanol (99).

on polysaccharide by using cellulose acetate TLC plate in 1973. In addition, other cellulose derivatives have been used for this purpose in TLC. Most commonly used cellulose derivatives are tisphenylcarbamate, 2,3-dichlorophenylcarbamate, 2,4-dichlorophenylcarbamate, 2,6-dichlorophenylcarbamate, 3,4-dichlorophenylcarbamate, 3,5-dichlorophenylcarbamate, 2, 3-dimethylphenylcarbamate and 3,5-dimethylphenylcarbamate. Aboul-Enein et al. (105) reviewed enantiomeric separations of racemates on polysaccharides chiral TLC plates. The authors discussed the role of the substituents of polysaccharides derivatives on chiral resolution. The effect of the substituents of cellulose derivatives and mechanisms of chiral resolution on these plates was found similar to HPLC separations. Faulpel (106) determined the chiral resolution capabilities of TLC, which resulted in its commercialization. These plates are stable in aqueous (acid or base) and non-aqueous mediums with the exception of glacial acetic acid and ketonic solvents like acetone and ethyl acetate. Other chiral resolutions on cellulose plates include oxindanac benzylester and 2-phenylcyclohexanone (107).

Xuan and Lederer (108) studied the enantiomeric resolution of substituted tryptophan derivatives on microcrystalline cellulose. The authors observed that aqueous solvents and liquid-liquid systems yielded essentially the same separations, suggesting that adsorption could play a role in liquid-liquid (partition) systems in some instances. Yuasa et al. (109–113) separated the enantiomers of DL-tryptophan and their derivatives by using crystalline cellulose as the chiral stationary phase in TLC. The authors tried to explain the chiral recognition mechanisms. They concluded that the helical form, which exist in different configurations in aqueous and non-aqueous media; for polysaccharides are responsible for chiral resolution. Suedee and Heard (114) reported the resolution of the enantiomers of β-blockers by using cellulose phenyl carbamate derivatives as the chiral stationary phase. Lepri et al. (115) described the resolution of 21 racemates on microcrystalline cellulose triacetate (MCTA) plates eluted with aqueous/organic mixtures containing methanol or ethanol or 2-propanol. Malinowska and Rozylo (116) used chitin and chitosan as TLC plate material for enantiomeric resolution of amino acids. The enantiomeric resolutions on TLC are given in Table 1.

COATED *VS* IMMOBILIZED CSPS

The extent of chiral resolution of enantiomers by liquid chromatography does not depend solely on chiral selectors but can be affected by a number of other parameters. Many racemates have been resolved on coated and immobilized polysaccharide chiral stationary phases simultaneously, which were found to be complimentary to each other. Some

racemates could be resolved on coated CSPs only while others are better resolved on the immobilized forms under the identical chromatographic conditions. However, the ability to use a wide range of solvents is an added advantage of immobilized CSP in comparison to the coated ones. Solvents such as tetrahydrofuran (THF), chloroform, dichloromethane, acetone, ethylacetate and methyl *tert*-butyl ether are prohibited with coated CSPs and cannot be used but immobilized CSPs can tolerate these solvents. Sometimes, the determination of kinetics, pharmacodynamics and reaction mechanisms involve the above-cited solvents and, hence, coated CSPs are not capable to work under such situations. On the other hand, immobilized CSPs can be used for such requirements and, therefore, immobilized CSPs have more wide range of potential applications.

To compare the working capabilities of the coated and immobilized CSPs, some authors attempted to carry out enantioseparation of various racemates on these CSPs. Oliveros et al. (117) immobilized five different derivatives of cellulose on silica gel and used for the chiral resolution of warfarin, lorazepam, oxazepam, tertatolol, propranolol, pindolol, naproxen, flubiprofen and nicardipine by using different combinations of heptane-2-propanol, heptane-2-propanol-diethylamine, heptane-2-propanol-trifluoroacetic acid, heptane-chloroform, heptane-chloroform-diethylamine and heptane-chloroform-trifluoroacetic acid solvents mixtures. The authors concluded that all CSPs were able to resolve most of the studied racemates but cellulose 4-methylphenylcarbamate derivative gave the best resolution.

Zhang et al. (8) compared the chiral separation of bupivacaine racemate under identical chromatographic conditions [mobile phase-acetonitrile-diethylamine (100:0.1, v/v)] on Chiralpak AD (coated) and Chiralpak IA (immobilized) columns and the authors reported better resolution on later column. Chen et al. (118) studied a comparison of chiral recognition of immobilized CSPs and reported that the chemically bonded type CSPs were found to be relatively more stable with solvents such as tetrahydrofuran (THF) and chloroform into the mobile phase. The choice of solvents used was greatly extended and better resolution of several test enantiomers was observed on the immobilized CSPs with the addition of THF and chloroform to the mobile phase. Aboul-Enein et al. (53, 119) compared the chiral recognition capabilities of Chiralpak IA column with Chiralpak AD for a variety of racemates and noted a complimentary working nature of these two columns i.e. in some cases Chiralpak AD column was found better while in other cases Chiralpak IA gave the best results. Chen et al. (120) performed the enantiomeric separations of *tris*-(2-phenylpyridine) iridium (III) complexes on Chiralpak IA column by using *n*-hexane-$CHCl_3$-CH_2Cl_2 (75:20:5, v/v) as an eluent. Nadalini et al. (121) studied the chromatographic behavior

of a set of racemic dihydropyrimidines (DHPMs) on two polysaccharide chiral stationary phases under normal phase conditions. One of these is coated and the other chemically immobilized.

Ghanem et al. (122) compared enantiomeric resolution of cyclopropen derivatives on both Chiralpak IA and Chiralpak AD by using a mixture of *n*-hexane-2-propanol (90:10 and 99:1, v/v) as mobile phase, which is shown in Figure 10, which indicates good resolution of some derivatives on Chiralpak IA and some on Chiralpak AD. This sort of behavior compels us to conclude the complimentary nature of these columns. The solvent versatility of Chiralpak IA was investigated for the enantioselective separation of a set of cyclopropane derivatives using ethyl acetate or dichloromethane (DCM) as non-standard mobile phase

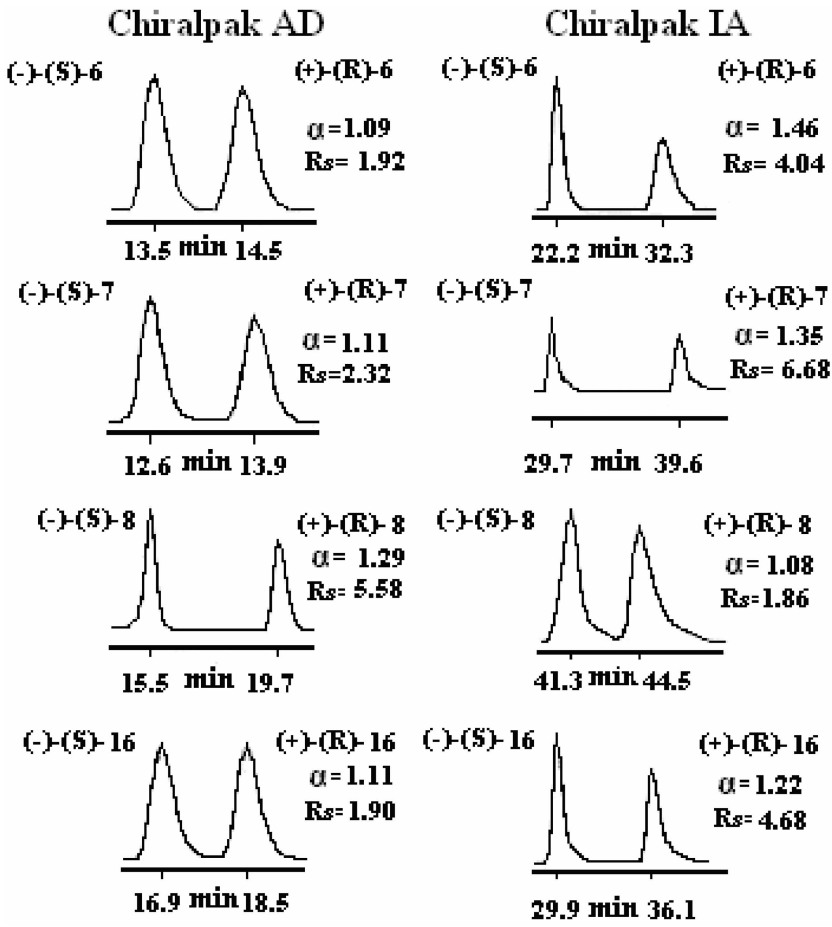


Figure 10. A comparison of enantiomeric resolution of cyclopropen derivatives on both Chiralpak IA and Chiralpak AD (122).

eluent and diluent. Furthermore, Ghanem et al. (123) compared the enantiomeric resolution of racemic *N*-alkylated barbiturates and thalidomide analogs on both immobilized and coated CSPs i.e. Chiralpak IA and Chiralpak AD, respectively, by using a mixture of *n*-hexane-2-propanol (90:10, v/v) as mobile phase. The authors observed that Chiralpak IA as superior phase; possessing a high resolving power in most of the reported cases. Furthermore, the same authors (124) studied the direct enantio-separation of a set of racemic *N*-alkylated barbiturates and analogs of thalidomide by using Chiralpak IB with different non-standard solvents such as dichloromethane (DCM), ethyl acetate, THF, methyl *tert*-butyl ether as an eluent and diluent. The authors also compared the separation, elution and resolution of the compounds on both immobilized and coated cellulose CSPs (Chiralpak IB and Chiralcel OD), respectively, and concluded that the Chiralcel OD column possesses a high resolving power in some cases than the immobilized one. However, few racemates, were resolved better on Chiralpak IB. The chiral separations on immobilized polysaccharide chiral phases are summarized in Table 1.

A COMPARISON OF CSPS COMMERCIALIZED BY DIFFERENT COMPANIES

We, the authors have been working since 1987 in the area of chiral separations of various racemates by liquid chromatographic and have quite enough experience, observation and dictations by scientific experiments. We have used all most all chiral commercial columns of above mentioned companies under normal and reversed phases modes. To the best of our knowledge and experience CSPs supplied by Diacel are the best ones followed by Kromasil, Macherey Nagel and Knauer. To the best of our knowledge these columns are comparable to the Daicel columns and are available with different dimensions and silica particle sizes. Moreover, these columns have some advantages (125, 126) over those supplied by others, which include:

- Inexpensiveness.
- Available on 5 and 3 μm silica gel particle sizes.
- No pressure limit and can work up to more than 300 bars.
- Quick regeneration after using acidic and basic mobile phase additives.
- Fast separations as 7.2 mL/min. flow rate can be used with 5 cm long column.

The application note of Kromasil (104) represents the chiral separations of a variety of racemates by using these columns under both normal and reversed phase modes. The various classes of racemates separated

include β-blockers, profens, alkaloids and other chiral drugs. The mobile phases used were different combinations of alkane and alcohols with acidic and basic additives in normal phase mode. The separations were achieved within 2 to 15 minutes in most of the cases. The mobile phase recommended in reversed phase modes were different combinations of phosphate buffer and acetonitrile and acetonitrile and water. The separations were observed in short analysis time than in case of normal phase. It is interesting to observe that the peaks are very sharp with base line separation in these CSPs. Some important applications of these CSPs are summarized in Table 1. Attempts have been made to observethe and compile the capabilities of chiral separations by CSPs of other companies and are included in Table 1, which gives a nice comparision of chiral selectivities of different columns supplied by various companies.

CHIRAL RECOGNITION MECHANISM

The enantiomeric recognition mechanism is one of the most important issues for chiral analytical scientists for applying polysaccharides CSPs properly and more precisely. But the chiral recognition mechanism at a molecular level on these CSPs is still not clear. Even though some experimental data support that chiral resolution is achieved through different types of bondings on the chiral grooves of polysaccharides CSPs. Hesse and Hagel (127) and Francotte et al. (57) suggested an inclusion mechanism on the chiral grooves of the CTA-I matrix. Other theoretical (128) and X-ray studies of the model compound, fully acetylated D-glucopyronose-(R)-phenylethyl amine inclusion complex also supported the inclusion mechanism. The main chiral sites of bondings are polar carbonyl groups of esters which can interact with racemic compounds through hydrogen bonding and dipole-dipole interactions for chiral discrimination (25). Wainer and Alembic (129) supported the above facts by studying a series of aromatic amides and alcohols (130) on CTB phases. Most important adsorbing site on the phenylcarbamate derivatives are polar carbamate groups; capable of interacting with a racemic compound by hydrogen bonding with –NH- and >C=O groups and the dipole-dipole interaction on >C=O (26).

Yashima et al. (131) has concluded that -NH- and >C=O groups are most important bonding sites. Furthermore, these authors extended their work (132) and compared the chiral recognition between cellulose *tris*-(phenylcarbamate) (CTPC) and cellulose *tris*-(3,5-dimethylphenylcarbamate) (CDMPC) using *trans*-stilbene oxide and benzoin as the racemates. The calculations of interaction energies between cellulose *tris*-(phenylcarbamate) (CTPC) or cellulose *tris*-(3,5-dimethylphenylcarbamate)

(CDMPC) and *trans*-stilbene oxide or benzoin were performed by various methods using force fields. The results indicated that the polar carbamate residues of cellulose derivatives might be most important adsorbing site for polar racemates and may play a crucial role in chiral recognition. Aboul-Enein and Ali (133) carried out studies on the chiral resolution of methylphenidate on polysaccharide CSPs and observed that π-π interactions were also the important binding forces for the chiral resolution of aromatic racemates. The best resolution of methylphenidate (MPH) on Chiralcel OB column was achieved when phenol or benzoic acid, separately, were used as mobile phase additives. Phenol or benzoic acid form the MPH-phenol or MPH-benzoic acid pairs in which the possibility of π-π interaction between these pairs and CSP is greater than the possibility of π-π interactions between MPH and CSP. Therefore, the improved resolution of MPH enantiomers occurred, when using phenol or benzoic acid as the mobile phase additives, by an enhancement of π-π interactions. Similarly, these authors (134) also observed that coordination bonding also plays an important role for the chiral resolution of the racemates having sulfur atom.

Figure 2 clearly shows the presence of chiral grooves on amylose and cellulose materials, which provide chiral pocket to the enantiomers. The electronegative atoms such as oxygen, nitrogen and halogens of racemates form hydrogen bondings and dipole-dipole induced interactions within these grooves. Besides, π-π interactions also occur between phenyl ring of aromatic racemates and the CSP. During chiral resolution, the enantiomers fit stereogenically in the different fashions into the chiral grooves of the CSP which is stabilized by various types of bondings (as discussed above) of different magnitudes and, hence, the resolution of enantiomers occurred. In addition to these bondings, steric effect also governs the chiral resolution on polysaccharide CSPs. Besides, some other achiral weak bondings like Van der Waal forces may also contribute in the chiral resolution.

POLYSACCHARIDE CSPS AND CHIRAL DRUGS DEVELOPMENT

After issuing certain guidelines by U.S. F.D.A. and European agencies the concept of chirality in drugs development has achieved recent attention; specially for marketing of optically active (homochiral) drugs. But, sometimes, homochiral drug enantiomer may racemize into human body leading to the generation of other antipodes, which may be toxic or ballast to the human beings. Besides, racemization reduces the administrated dosage concentration as optically active enantiomer converted into its inactive one. Therefore, enantioselective study of homochiral

drugs is an important and urgent need of human friendly medication. For this type of medication, the detail studies on chiral separation, enantioselective toxicology, pharmacodynamics and stereoselective interactions with receptors are very much required, which require effective CSPs. And, of course, as discussed above polysaccharide based CSPs have a wide range of applications and great potential to study the above cited enatio-selective behavior of enantiomers. Moreover, the introduction of immobilized CSPs has make this task easy as the enantioselective analyses can be carried out in any type of biological fluids and medium. Briefly, polysaccharide CSPs are the boon in the area of the chiral drugs development. Some reviews (7, 135–140) have appeared in the literature describing chiral drug development involving the use of various CSPs including polysaccharide based ones. The work of some scientists on chiral drugs development by using polysaccharide CSPs is discussed in the following section.

Kroemer et al. (141) described an enantiomer-enantiomer interaction of (S)- and (R)-propafenone modifies; the effect of racemic drug therapy. The authors used Chiralpak AD column for this purpose. The blood samples were taken after 0.5, 1, 1.5, 2, 2.5, 3, 4, 6 and 24 hours after the administration of propafenone. The authors reported that the pharmacological activity and toxicity profile of a racemate may be modulated by enantiomer-enantiomer interactions. Lanchote et al. (142) discussed enantio-selective concentrations of metoprolol in human plasma by using solid phase extraction and Chiralpak-AD and Chiralcel-OD-H columns. The correlation coefficients of the enantiomers in plasma were 5-223 ng/mL. Kim et al. (143) presented a method for monitoring fate of enantiomers of metoprolol in human urine samples. Authors used liquid-liquid extraction followed by chiral HPLC. The column used was Chiralcel-OD and the detection limit achieved was 25 ng/mL. Kanzawa et al. (144) also studied metabolism of loxoprofen enantiomers in human plasma on Chiralcel OJ column; after the administration of the therapeutic dose of the racemic drugs. Teng et al. (145) studied the fate of flurbiprofen enantiomers in rat serum on Chiralpak AD-RH column.

Masetto de Gaitani et al. (146) described the degradation of thioridazine (THD) and thioridazine 2-sulfone (THD 2-SO_2) in human plasma by using Chiralpak AD and Chiralcel OD-H columns. The authors reported that both enantiomers of THD and THD-2-SO_2 were stable at varying temperatures, pH and ionic strengths. The solubility of THD and THD 2-SO_2 enantiomers were observed at pH 8.5. The influence of light on the stability of the THD and THD 2-SO_2 enantiomers was also studied and the degradation of THD enantiomers was observed at 254 and 366 nm while THD-2-SO_2 enantiomers were stable at these wavelengths. Teng et al. (145) studied pharmacokinetic of flurbiprofen in biological fluids by using Chiralpak AD-RH column.

Cerqueira et al. (147) developed the chiral resolution method of α-hydroxymetoprolol in human plasma and urine. The authors used solid phase and liquid-liquid phase extractions techniques for the isolation from plasma and urine respectively. The chiral column used was Chiralpak-AD with *n*-hexane-ethanol-isopropanol-diethyleamine (80:10:2:1.8:0.2, v/v) as mobile phase for plasma sample and n-hexane-ethanol-diethyleamine (88:12:0.2, v/v) for urine sample separately and respectively.

Aboul-Enein et al. (148) studied the chiral inversion of ketoprofen in horse plasma by using of Chiralcel OJ-R column and concluded that the chiral inversion of R-ketoprofen to S-ketoprofen is significant in equine species. Furthermore, Aboul-Enein and Ali (149) studied enantioselective interactions of cromakalim; an anti-hypertensive drug (potassium channel activator); with plasma proteins. The authors reported strong binding of (-)-chromakalim, which is pharmacologically active enantiomer. The columns used were Chiralpak AD-R, Chiralcel OD-R and Chiralcel OJ-R. The mobile phases used were water-acetonitrile (70:30, v/v) for Chiralpak AD-R and Chiralcel OD-R columns and water-acetonitrile (80:20, v/v) for Chiralcel OJ-R column. The concentration of cromakalim in human plasma was determined by using solid phase extraction method. Papini, et al. (150) described kinetic disposition of lorazepam with focus on the glucuronidation capacity, transplacental transfer in parturients and racemization in biological samples. The study was conducted on 10 healthy patients, aged 18–37 years with a gestational age of 36-40.1 weeks, treated with a single oral dose of 2 mg racemic lorazepam 2-9 h before delivery; with collection of blood samples over a 0-48 h interval and the umbilical cord sample was obtained immediately after clamping. The enantiomeric resolution of lorazepam was carried out by LC-MS/MS using a Chiralcel OD-R column. As per authors, pregnancy changed the pharmacokinetics of lorazepam enantiomers with respect to occurrence of an increase in the apparent distribution volume, an increase in apparent oral clearance and a reduction in the elimination half life. Mateus et al. (151) described a reduction of enantioselectivity in the kinetic disposition and metabolism of verapamil and norverapamil in rats. The blood samples collected from the tail up head after 6 h verapamil administration, which were analyzed by LC-MS/MS on Chiralpak AD column.

POLYSACCHARIDE CSPS AND CHIRAL XENOBIOTICS

In recent years the concept of chirality has attracted environmental scientists. Ali et al. (5, 152) has exposed the importance of chirality in the environmental science having written the first book on chiral pollutants.

Many xenobiotics are chiral in nature having different toxicities and, hence, the determination of the exact toxicities of such pollutants needs the concentrations of individual antipodes. As usual some CSPs have been used to study the chiral ratio of different xenobiotics including polysaccharide CSPs. Some papers describing the utility of polysaccharide CSPs in the environment are described herein. Ali and Aboul-Enein (153) separated *o,p*-DDT and *o,p*-DDD chiral pesticides on Chiralpak AD-RH, Chiralpak OD-RH and Chiralpak OJ-R with acetonitrile-water (50:50 v/v) and acetonitrile-2-propanol (50:50 v/v) as mobile phases. Caccamese and Principato (154) reported the chiral resolution of four enantiomeric paires of vincamine alkaloids by using Chiralpak AD column with *n*-hexane-2-propanol and *n*-hexane-ethanol mobile phases. The authors concluded that (+)-*cis*-vincamine eluted much faster as compare to the other optical isomers. Ellington et al. (128) described enantio-separation of organophosphorus pesticides (dialifor, fonofos, fenamiphos, fensulfothion, isofenphos, malathion, methamidophos, profenofos, crufomate, prothiophos and trichloronate) with heptane and ethanol as mobile phase on Chiralpak OD, OJ, AS, AD and Chiralcel OG as chiral selectors. Li et al. (155) performed the chiral resolution of phenthoate in soil samples. The authors used Chiralcel OD chiral column with hexane-2-propanol (100: 0.8, v/v) as mobile phase.

Xu and co-workers (156) reported chiral separation and aquatic toxicity of enantiomers of the pyrethroid insecticide λ-cyhalothrin. The columns used were Chiralpak AD, Chiralpak AS, Chiralcel OD and Chiralcel OJ with ethanol and isopropanol as eluent modifiers. Kim et al. (157) studied enantiomeric separation of pyrethroic acid methyl and ethyl esters on Chiralcel OD and Chiralcel OF columns with hexane-2-propanol as mobile phase. The author observed greater chiral resolution capability of Chiralcel OD than Chiralcel OF column. Furthermore, the same authors (158) resolved aminothiazolecarboxamide fungicide (ethaboxam) on Chiralcel OD, Chiralcel OD-H and Chiralpak AS columns. Lin et al. (159) determined stereoisomeric separation and toxicity of the nematicide fosthiazate. All four stereoisomers of fosthiazate were separated successfully with a Chiralpak AD and Chiralpak AD-R columns. Recently, Jiang et al. (160) described the chiral separation of pyrethroid cycloprothrin xenobiotic along with its stereo-selective insecticidal activity. The columns used were Chiralcel OJ-H and Chiralcel OD-H. Li et al. (161) reported enantiomeric separation and aquatic toxicity of 1-(substituted phenoxyacetoxy)alkylphosphonate herbicide enantiomers. The chiral columns applied for this work were Chiralpak AD, Chiralpak AS, Chiralcel OD and Chiralcel OJ. The chiral separations were optimized by varying the composition of mobile phase and experimental temperature. Some of the applications of polysaccharide CSPs in the chiral separations of xenobiotics are summarized in Table 1.

CONCLUSION

The origin of polysaccharide CSPs has a long history but the commercial columns came into the market in 1980s and since then these CSPs have become the leaders in chiral separations. These CSPs have given a great impetus to chiral drugs developments. The immobilization of these CSPs has made possible the determination of various enantiomer-enantiomer interactions in different matrices; responsible for developing and designing homochiral drugs. Besides, immobilized CSPs can be used to monitor certain stereospecific reactions, which are only possible to carry out in polar solvents. In addition to this, these CSPs may be useful to ascertain chiral recognition mechanisms and monitoring stereo-controlled reactions; carried out in prohibited solvents such as tetrahydrofuran, chloroform, dichloromethane, acetone, 1,4-dioxane, ethylacetate and methyl *tert*-butyl ether. Of course, these CSPs are quite developed but still not capable to separate racemates at preparative scale (kilogram quantities), which is the urgent need of pharmaceutical industries. We would like to mention here that the Government and controlling authorities of some developing countries of Asia and Africa continents should come forward to introduce the homochiral drugs for better lives of the public. Briefly, polysaccharide CSPs should be developed more; capable to resolve racemates at kg levels; and the concept of homochiral drugs must be introduced all over the world including developing and under developed countries.

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