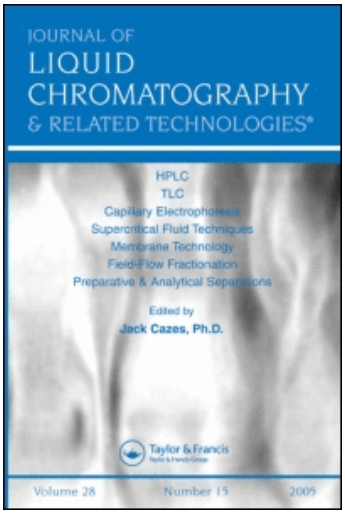

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Structural Factors Affecting Chiral Recognition and Separation on Cellulose Based Chiral Stationary Phases

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STRUCTURAL FACTORS AFFECTING CHIRAL RECOGNITION AND SEPARATION ON CELLULOSE BASED CHIRAL STATIONARY PHASES

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A B S T R A C T

The structural factors and functional group selectivity requirements affecting direct high-performance liquid chromatographic enantiomeric resolution of drug racemates on several derivatized cellulose chiral stationary phases are reviewed.

A guide for the choice of the appropriate chiral cellulose derivative column based on elements of asymmetry and functional groups of the compounds are presented.

I N T R O D U C T I O N

Many of the drugs used in clinical practice are chiral, that is they exist as enantiomeris, which are mirror images and are related to one another in the way that the left hand is related to the right.

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Most of these drugs (over 80%) are administered as racemates (mixtures of the R & S enantiomers) (1) for the following reasons: a) The synthetic method produces a racemate mixture and separation may be too expensive, or b) In case of new developed drug, the techniques for separation of the two enantiomers are not yet developed, or c) The benefit of administration of an optically pure enantiomer of a specific drug may not have been proven. The individual enantiomers of such racemate mixture frequently differ in pharmacological, metabolic activities (2) and pharmacokinetic behaviour (3) and often only one enantiomer is therapeutically active. These pharmacological and biological differences between enantiomers of a given drug may be due to several factors, for example enantiomers may interact differently with optically active components of the living cells (receptors, enzymes, proteins) leading to differences in pharmacokinetics and metabolism.

Owing to the increasing awareness of these biological differences between enantiomers (3,4,5,6,7), it is important to be able to separate and determine them in biological fluids. Even if a drug is given as a pure enantiomer, methods that can discriminate between enantiomers will be required because racemization can occur both in vitro (8) and in vivo (9).

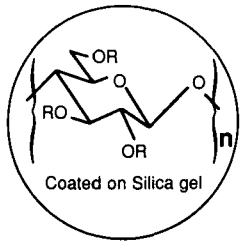
Although separation and quantification of enantiomers have been traditionally regarded difficult and time-consuming, recently research work has been carried out in devising efficient, simple, and direct ways for enantiomeric separation and analysis particularly using high-performance liquid chromatography (HPLC) with chiral stationary phases (CSPs). Several chiral stationary phases have now become commercially available for direct resolution of racemates without derivatization. Chiral stationary phases represent one of the most significant developments in this field and become a major tool of analysis of enantiomers.

Dappen et. al. (10) have discussed in details the applications and proposed a classification for CSPs based on separation principles. Blaschke described the use of cellulose, starch and cellulose acetate as chiral sorbant (11).

This article will discuss the structural features required for chiral recognition using cellulose-derived CSPs which belong to the helical polymer phases.

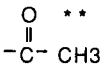
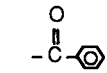
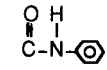
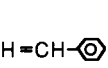
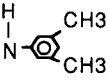
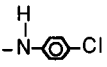
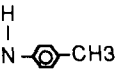
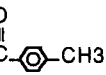
TABLE I

Structure of Derivatized Cellulose known as Chiralcel *



* These phases are available from Daicel Chemical IndustriesLtd., Tokyo, Japan

** If the phase is packed as a fine powder, the column is known as Chiralcel CA1.

CHIRALCEL COLUMN	R
OA	
OB	
OC	
OK	
OD	
OF	
OG	
OJ	

Recently several cellulose derivatives (e.g. esters, ethers and carbamates) have been developed, the structure of some of these CSPs are shown in Table 1. These derivatives can be used for enantiomeric separation of a large number of drugs.

Both polar solvents (methanol, ethanol) and non polar solvents (hexane, 2-propanol) are used as a mobile phases with these CSPs. Aquous mobile phase can also be used in some cases. The solute always competes with the modifier for hydrogen bonding sites on the CSP. This competition takes place at both chiral and achiral sites on the CSP (12). This does not preclude interaction between the modifier and the solute, which appears to play a lesser role in the determination of the chromatographic parameters. However, chlorinated solvents such as chloroform and methylene chloride and solvents such as benzene, toluene, ethyl acetate, acetone and acetonitrile will cause damage to the packing mate-

rial of these columns, since they tend to strip the derivatized cellulose from the silica support and should be avoided.

Structural Factors Affecting Chiral Separation of Enantiomers on Cellulose Derivatives:

A large number of chiral drugs such as benzodiazepines were resolved on optically active microcrystalline cellulose acetate (13).

Okamoto and co-workers (14,15) have tested several silica-based cellulose triphenyl carbamate derivatives as CSPs for optical resolution of β-blockers, alkaloids and other compounds with a mobile phase of 0.1% diethylamine in hexane:2-propanol (4:1). Cellulose tris (3,5-xylylcarbamate) and cellulose tris (3,5-dimethylphenyl carbamate) stationary phases were found most suitable for optical resolution of β-blockers and alkaloids, respectively, providing optimum separation.

The interactive sites are located within the chiral cavities of the helical structure of the cellulose derivatives. The main chiral recognition sites are considered to be the polar carbamate and ester groups, which can interact with a solute via hydrogen bonding or dipole-dipole interactions. These interactions may further be influenced by the nature of the substituents on the phenyl groups of the solute. The chiral recognition can also takes place through an alteration of the steric environment of the chiral cavity due to the formation of an inclusion complex with the CSPs. A recent study by Wainer et. al. (16) has demonstrated that with the tribenzoate form of the CSP an increase in the steric bulk around the hydroxyl moiety of the modifier tends to result in increased retention and stereoselectivity in a series of enantiomeric amides. This is a result of either (1) the competition for binding to the chiral sites of the CSP, (2) the binding of the mobile phase modifier to the achiral sites near or at the chiral cavities of the CSP, which alters the steric environment of these cavities, or (3) to a combination of both of these phenomenon.

Most compounds successfully separated on these phases contain a phenyl, carbonyl, nitro, cyano, sulfonyl or hydroxyl group. The type of nitrogen function

present in the target molecule is one of the initial considerations when chosing the appropriate CSP. It is at this point that the chromatographer must decide whether or not to derivatize the solute and what type of derivative to make. These kind of cellulose columns are not recommended for use with primary, secondary and tertiary amines without precolumn derivatizations to a neutral function such as an amide. An α-amino acid or structurally related to an α-amino acid solutes are not suitable for these columns. Another initial consideration is the substitution at the chiral centre. If the nitrogen function is at the chiral centre these columns can be recommended otherwise not. When an aromatic ring is attached to the chiral centre then these column can be used. However, there are few applications, when the aromatic group is not at the chiral centre.

Although the crystallinity of the cellulose was shown not to be critical for chiral recognition (17), the molecular mass of the cellulose derivative, the solvent used for depositing the phase on the support and the nature of the support were found to have an effect on chiral separation.

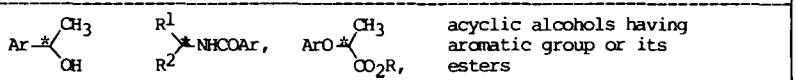
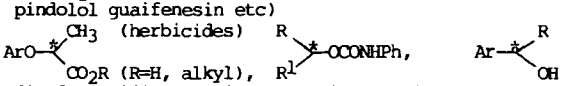
Among examples of chiral separation on these phases are those of β-adrenergic blockers separated on tris (3,5-dimethylphenyl carbamate) cellulose (14,18) known as Chiralcel OD phase.

Although many β-adrenergic blockers are developed and marketed as a racemic mixture of both enantiomers, for some of them only one enantiomer, usually the S-enantiomer, is therapeutically preferred (19), so it is important to assess their enantiomeric purity.

Since many of these cellulose derivatives are now commercially available* and in order to eliminate time-consuming trials to separate enantiomers, a guide for column selection of Chiralcel stationary phases was developed and shown in table 2 based on general structural and molecular features of the compounds (20). Also the first choice column based on element of asymmetry was derived from previous enantiomeric separation of drugs, agrochemicals and other organic com-

* Chiral columns are available from Daicel Chemical Industries Ltd, Tokyo, Japan

TABLE 2. GUIDE FOR COLUMN SELECTION FOR CHIRALCELS CHIRAL STATIONARY PHASES (CSP's)

COLUMN	GENERAL STRUCTURAL FEATURE	EXAMPLES OF PARTICULAR MOLECULAR STRUCTURAL FEATURES
OA	small aliphatic compounds	cyclic carbonyl compounds (lactones, 4-hydroxycyclopentenone)
OB	small aliphatic compounds	cyclic ketones, lactones, sulfoxides, amides, diol diacetates
	small aromatic compounds	 acyclic alcohols having aromatic group or its esters
OC OG OF	cyclopentenones	4-siloxy (OC, OG) or 4-alkoxycarbonylmethyl (OC) cyclopentenones
	aromatic compounds	β-lactams, tetrahydroquinoline alkaloides, biphenyl atropisomers, sulfoximine benzazepine drugs, dihydropyridine derivatives e.g. Ca^{+2} channel blockers (OG, OF)
OD	aromatic compounds	amines containing aromatic ring(s), alkaloids (tetrahydroquinoline alkaloids, atropine, homatropine, tetrahydropalmatine). ArO-CH_2-CH(OH)-R (β-blockers. e.g. alprenolol, practolol, propranolol, pindolol guaifenesin etc)  (herbicides) dihydropyridine (antihypertensives), binaphthol analogs
OJ OK	aromatic compounds	 (R=H, alkyl. antiinflammatory agents, OJ), (herbicides) cyclic imides containing aromatic substituent (central depressants) dihydropyridine (antihypertensives, OJ) aryl thiophosphates (insecticides, OJ)
CA-I	aliphatic compounds	lactones, cyclohexanones
	aromatic compounds	helically condensed aromatic hydrocarbones, biphenyl atropisomers, cyclophanes, aromatic amide atropisomers, cyclic polyenes, Ar-C*-CO (barbiturates, hydantoins, cylicimides e.g. glutethimide, esters of arylcyanoacetic acids etc)

• Indicates the position of the chiral carbon.

TABLE 3. FIRST CHOICE OF CHIRALCEL COLUMN BASED ON ELEMENT OF ASYMMETRY

ELEMENT OF ASYMMETRY	COLUMN
- C_2 symmetric aromatic compound	OT, CA-I
- planar chiral compound	CA-I, OD
- asymmetric carbon center (next to)	
a) aliphatic compounds bearing C=O, NO_2, CN, C-O-C	OB, OA
b) aromatic compounds with	
- flexible chain bearing aromatic group(s)	OB, OD
- cyclic chain bearing aromatic group(s)	OD, OF, OG, OC
- sterically congested aromatic compound	OD, OJ
- amine drugs bearing aromatic group(s)	OD, OF, OG, OC
- sulfur asymmetric centre	
sulfoxides	OB, OC
- phosphorous asymmetric center	
arylthionphosphate	OJ

pounds is shown in table 3. Both tables 2 and 3 can be used to select the appropriate cellulose CSPs for the racemate drug under investigation. Since at present there is no chiral bonded phases capable of separating all classes of compounds, and since most chiral columns are expensive compared to conventional column, it is important to select the most suitable phase to avoid unnecessary expenses and frustrating unsuccessful trials.

In summary, this article gives a better understanding for the overall structural group selectivity requirements and general guidelines for the choice of a suit-

able Cellulose derivatized CSP column that are commercially available, to be used for successful enantiomeric separation and analysis of drugs. Applications of these guidelines will be useful to analysts in this field.

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