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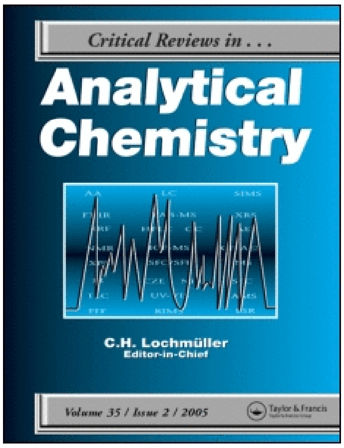

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Chiral Resolution of Racemic Environmental Pollutants by Capillary Electrophoresis

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The chiral resolution of environmental pollutants is an urgent need of today. Therefore, the chiral resolution of the environmental pollutants by capillary electrophoresis was reviewed. Various aspects of the chiral resolution by capillary electrophoresis such as chiral selectors, optimization of capillary electrophoresis conditions [composition of the back ground electrolyte (BGE), pH of the BGE, ionic strength of the BGE, structures and types of the chiral selectors, applied voltage, temperature, structures of the chiral pollutants, use of organic modifiers and other parameters, optimization by dependent variables], detection, sample treatment, validation of the methods and the chiral recognition mechanisms have been discussed.

Keywords Capillary electrophoresis, back ground electrolyte, chiral resolution, chiral environmental pollutants, optimization, chiral recognition mechanisms

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INTRODUCTION

Much work has been carried out on the chiral resolution of drugs, pharmaceuticals and agrochemicals but only few reports are available on the chiral resolution of the environmental pollutants (1–6). It has been reported that one of the two enantiomers of the chiral pollutant/xenobiotic may be more toxic (7). This is important information for the environmental chemist when performing environmental analysis. as the data of the simple analysis do not distinguish which mirror images of certain pollutants are more toxic and therefore more harmful. Biological transformation of the chiral pollutants can be stereoselective—uptake, metabolism, and excretion of enantiomers may thus be very different (7, 8); therefore, the enantiomeric composition of the chiral pollutants may be changed in these processes. Metabolites of the chiral pollutants often are chiral. Thus, to obtain information on the toxicity and biotransformation of the chiral pollutants it is necessary to develop a suitable method for the chiral resolution of the environmental pollutants. In view of this, a diverse group of people ranging from the regulators, to the people in material industries, clinicians and nutritional experts, agriculture experts and environmentalists, are now demanding data on the ratio of the enantiomers of the chiral pollutants to their total concentration.

Most often gas chromatography (GC) and high performance liquid chromatography (HPLC) have been used for the chiral resolution of the environmental pollutants. But the high polarity, low vapor pressure and derivatization in some of the environmental pollutants are the factors that complicate GC analysis. On the other hand, due to the inherent limited resolving power of conventional HPLC techniques, optimization of the chiral resolution of the pollutant often involves complex procedures or numerous experiments leading to the consumption of large amount of solvents and sample volume (9). Moreover, the efficiency in HPLC is limited due to the profile of the laminar flow, mass transfer term and possible additional interactions of enantiomers with the residual silanol groups of the stationary phase. Presently, capillary electrophoresis (CE), a versatile technique of high speed and sensitivity, is a major trend in analytical science and some publications on the resolution of the chiral environmental pollutants have appeared in the recent years. The high efficiency of CE is due to the flat profile originated and to a homogeneous partition of the chiral selector in the electrolyte, which in turn, minimizes the mass transfer. Hernandez-Borges et al. (10) reported an overview on the applications of CE to

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the chiral analysis of pollutants and their metabolites. The main advantages and drawbacks regarding the use of CE for chiral separation of pollutants were addressed including some discussion on the foreseen trends of electromigration procedures applied to chiral analysis of contaminants. Recently, Wong (11) reviewed the analytical chemistry, environmental occurrence, and fate aspects of stereoisomers of chiral pollutants. The authors advocated the use of mass spectrometry (MS) and tandem mass spectrometry (MS/MS) as detectors in analytical techniques including CE. Therefore, attempts have been made to explain the art of the enantiomeric resolution of the chiral environmental pollutants by CE. The present review discusses the chiral resolution of the environmental pollutants by CE describing various aspects of the chiral resolution, i.e., chiral selectors, optimization of capillary electrophoresis conditions [composition of the back ground electrolyte (BGE), pH of the BGE, ionic strength of the BGE, structures and types of the chiral selectors, applied voltage, temperature, structures of the chiral pollutants, use of organic modifiers and other parameters, optimization by dependent variables], detection, sample treatment, validation of the methods and the chiral recognition mechanisms.

CHIRAL SELECTORS

As in the cases of GC and HPLC, a chiral selector is also required in CE for the enantiomeric resolution. Generally, the suitable chiral compounds are used in BGE as the additives and hence are called as chiral selectors or chiral BGE additives. There are only, a few publications available which deal with the chiral resolution on chiral capillary (on coated capillary by the chiral selector) in CE (12). The enantiomeric resolution of the chiral pollutants, discussed in this review, restricts the use of the chiral selectors in the BGE. CE as the chiral resolution technique has been used widely for the enantiomeric resolution of drugs and pharmaceuticals (13). Several reviews have also appeared on this issue, which describe the use of many chiral compounds as the chiral BGE additives (14–21). Therefore, the chiral compounds used as BGE additives reported in these reviews and other publications may be used for the enantiomeric resolution of the chiral pollutants also. The most commonly used chiral BGE additives are cyclodextrins, macrocyclic glycopeptide antibiotics, proteins, crown ethers, ligand exchangers, alkaloids (14–24), etc. A list of these chiral BGE additives is presented in Table 1. α-, β- and γ-Cyclodextrins and their derivatives have been used frequently in chiral CE because these chiral selectors are water soluble, having functional groups and cavities responsible for diastereomeric inclusion complexes formation with the chiral pollutants.

The basic requirements for a suitable chiral selector applied in CE include:

- inexpensive and universal in use along with its solublity and stability in BGE;
- having sufficient groups, atoms, grooves, cavities, etc. for complexing with chiral pollutants;
- should increase EOF, or at least it should not effect EOF;
- pollutant diffusion through the chiral selector, specific selector-selectand and interactions, and accordingly, mass transfer kinetics must be favorable in order to effectively employ the advantages offered by the electrically driven flow;
- should have suitable chemoselectivity in combination with enantioselectivity as it may be used for the resolution of structurally related pollutants; and
- non-UV absorbing in nature as, generally, the detection in CE is carried out by UV detector.

TABLE 1
The most commonly used chiral selectors

Chiral selectors (chiral BGE additives)	Refs.
Cyclodextrins	13, 17–19
Macrocyclic glycopeptide antibiotics	13
Proteins	13, 20
Crown ethers	13, 23
Alkaloids	13, 22
Polysaccharides	3, 13
Calixarenes	3, 13
Imprinted polymers	24
Ligand exchangers	24

APPLICATIONS

For a few years, CE has been used for the chiral resolution of pesticides, polynuclear-aromatic hydrocarbons, amines, carbonyl compounds, surfactants, dyes and other toxic compounds. CE has also been utilized to separate the structural isomers of various toxic pollutants such as phenols, polyaromatic hydrocarbons, etc. Weseloh et al. (25) investigated CE method for the resolution of biphenyls using phosphate buffer as BGE with cyclodextrin as chiral additive. Sarac et al. (26) resolved the enantiomers of 2-hydrazino-2-methyl-3-(3,4-dihydroxyphenyl) propionic acid using cyclodextrin as the BGE additive. The used cyclodextrins were native, neutral and ionic in nature with phosphate buffer as BGE. Miura et al. (27) used CE for the chiral resolution of seven phenoxy acid herbicides using methylated cyclodextrins as the BGE additives. Furthermore, Tsunoi et al. (28) resolved these pesticides, i.e., MCPP, DCPP , 2,4-D, 2,4-CPPA, 2,4,5-T, 2,3-CPPA, 2,2-CPPA , 2-PPA and silvex, using cyclodextrins with negatively charged sulfonyl groups as the chiral BGE additives. Gomez-Gomar et al. (29) investigated the simultaneous enantioselective separation of (±)-cizolirtine and its impurities: (±)-N-desmethylcizolirtine, (±)-cizolirtine-*N*-oxide and (±)-5-(-hydroxybenzyl)-1-methylpyrazole by CE. An application of on-line coupling of CE and MS (CE-MS) to the chiral separation of phenoxy acid herbicide enantiomers was investigated by Otsuka et al. (30). As an ionization method, electrospray ionization (ESI) is used for a CE-MS interface. Generally, non-volatile additives in separation solutions, decrease the MS sensitivity and/or signal intensity. However, heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin (TM-β-CD) was used as a chiral selector which migrated directly into the ESI interface. Using the negative-ionization mode along with a methanol-water-formic acid solution as a sheath liquid and nitrogen as a sheath gas, stereoselective resolution and detection of three phenoxy acid herbicide enantiomers were successfully achieved with a 20 mM TM-β-CD in a 50 mM ammonium acetate buffer (pH 4.6). The four enantiomers of the herbicides mecoprop and dichlorprop were resolved using an ethylcarbonate derivative of β-cyclodextrin (β-CD) with three substituents per molecule of hydroxypropyl-β-CD and native β-CD (31). The performances of these chiral selectors have been quantified by means of two-level full factorial designs and the inclusion constants were calculated from CE migration time data. Klein et al. (32) resolved the stereoisomers of metolachlor and its two polar metabolites [ethane sulfonic acid (ESA) and oxanilic acid (OXA)] by using CE. The enantiomers of ESA and OXA were separated by using γ-cyclodextrin as chiral BGE [borate buffer, pH = 9 containing 20% methanol (v/v) and 2.5% gamma-CD (w/v)] additive. The maximum resolution of ESA and OXA enantiomers was achieved using a capillary temperature of 15°C and applied voltage of 30 kV. Jarman et al. (33) reported the separation of metalaxyl, imazaquin, fonofos, ruelene and dichlorprop by using CE with cyclodextrin as chiral selectors. As per the authors, CE has been found to be a simple, efficient and inexpensive way to determine the transformation of chiral pesticides in laboratory micro-organisms at 25–50 mg/L concentration. Polcaro et al. (34) used solid-phase extraction and capillary electrophoretic for the stereoselective analysis of aryloxypropionic and aryloxyphenoxypropionic acidic herbicides in ground and river waters. Vancomycin and γ-cyclodextrin were used as BGE as chiral selectors. The detection limits achieved were 0.1–0.13 ppb and 0.4–0.54 ppb for ground and river waters, respectively. The chiral resolution of the environmental pollutants by CE is summarized in Table 2. The actual chromatograms of the resolved enantiomers of phenoxy acid herbicides are shown in Figure 1.

OPTIMIZATION OF CE CONDITIONS

Generally, the chiral resolution by CE is very sensitive and is controlled by a number of parameters. The optimization factors are categorized into two classes: independent and dependent parameters. The independent parameters are under the direct control of the operator. These parameters include the choice of the buffer, pH of the buffer, ionic strength of the buffer, type of chiral selectors, voltage applied, temperature of the capillary, dimension of the capillary, BGE additives and some other parameters. Contrarily, the dependent parameters are those directly affected by the independent parameters and are not under the direct control of the operator. These types of parameters are field strength (V/m), EOF, Joule heating, BGE viscosity, sample diffusion, sample mobility, sample charge, sample size and shape, sample interaction with capillary and BGE, molar absorptivity, etc. Therefore, the optimization of the chiral resolution can be controlled varying all these parameters mentioned above.

Composition of the BGE

The BGE in CE is used to maintain a high voltage gradient across the sample containing solution in the capillary and this requires that the conductivity of the electrolyte should be higher than the conductivity of the sample. Therefore, buffers are used as the BGE in most of the CE applications. Besides, to control the pH of the BGE, the use of buffers is essential. The most commonly used buffers are phosphate, acetate, borate, ammonium citrate, tris, CHES, MES, PIPES, HEPES, etc. that are used with different concentrations and pHs. The electrolyte identity and concentration must be chosen carefully for the optimum chiral resolution of environmental pollutants. The selection of the BGEs depends on their conductivity and the type of the environmental pollutant to be resolved. The relative conductivities of different electrolytes can be estimated from their condosities (defined as the concentration of sodium chloride, which has the same electrical conductance as the substance under study) (49) . A wide variety of electrolytes can be used to prepare the buffers for CE. The low UV absorbing components are required for the preparation of the buffers, in case of a UV detector is supposed to be use. Besides, the volatile components are required in the case of MS or ICP detection methods. These conditions substantially limit the choice to a moderate number of electrolytes. pH of the BGE is also another factor which determines the choice of the buffers. For low pH buffers, phosphate and citrate have commonly been used although the later absorbs strongly at wavelengths <260 nm. For the basic buffers, borate, tris, CAPS, etc. are used as the suitable BGEs. A list of useful buffers along with pHs and working wavelengths are given in Table 3 (50).

Crego and Marina (9) and Gübitz and Schmid (24) reviewed the chiral resolution of environmental pollutants by CE and they described phosphate, borate, acetate, CHES and carbonate as the BGEs. Welseloh et al. (25) used 30 mM phosphate buffer of pH 2.4 as the BGE for the chiral resolution of biphenyl pesticides. Mechref and El Rassi (44) resolved phenoxy acid herbicides using 175 mM phosphate (pH 6.5) (44) and 200 mM borate (pH 10.0) buffers (46) as BGEs. Furthermore, Tsunoi et al. (28) used a mixture of 0.1 M borate and 0.05 M phosphate buffers (pH 9.0) as BGE for the chiral resolution of phenoxy acid herbicides. Therefore, the nature and the type of BGE depends on the racemic pollutants and the chiral selectors used.

pH of the BGE

pH of the BGE is the most important factor for optimizing the chiral resolution as it is responsible for the stabilities of the

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TABLE 2
The chiral resolution of environmental pollutants by capillary electrophoresis

Chiral pollutants	Sample matrix	Electrolytes	Detection	Refs.
Fenoprop, mecoprop & dichlorprop	—	20 mM tributyl-β -CD in 50 mM, ammon. acetate, pH 4.6	MS	30
2-Phenoxypropionic acid, dichloroprop, fenoxaprop, fluaziprop, haloxyfop & diclofop enantiomers	—	75 mM britton-robinson buffer with 6 mM vancomycin	—	35
Imazaquin isomer	—	50 mM sod. acetate, 10 mM dimethyl-β-CD, pH 4.6	—	36
Phenoxy acid herbicides	—	200 mM sod. phosphate, pH 6.5 with various concns. of OG & NG	—	
Diclofop		50 mM Sod. Acetate, 10 mM trimethyl-β-CD, pH 3.6	—	36
Imazamethabenz isomers		50 mM Sod. acetate, 10 mM dimethyl-β-CD, pH 4.6	—	36
2-(2-methyl-4-chlorophenoxy) propionic acid,	—	0.05 M lithium acetate containing α- cyclodextrins	UV 200 nm	37
2-(2-methyl-4,6-dichlorophenoxy) propionic acid		0.05 M lithium acetate containing β-cyclodextrin	UV 200 nm	37
2-(2,4-dichlorophenoxy) propionic acid		0.05 M lithium acetate containing heptakis-(2,6-di-O-methyl)-β-cyclodextrin	UV 200 nm	37
2-(2-methyl-4-chlorophenoxy) propionic acid and 2-(2,4-dichlorophenoxy)- propionic acid	—	0.03 M lithium acetate containing heptakis-(2,6-di-O-methyl)-β-cyclodextrin	UV 200 nm	38
1,1′-Binaphthyl-2-2′-dicarboxylic acid, 1,1′-binaphthyl-2,2′-dihydrogen phosphate and 2,2′-dihydroxy-1-1′-binaphthyl-3,3′-dicarboxylic acid	—	0.04 M carbonate, pH 9.0, with non-cyclo-oligosaccharides	UV 215–235 nm	39
Ethofamesate	—	Buffer, pH 9 containing SBE-β-CD	—	40
Napropamide				
Phenoxy acid	—	0.1 M phosphate buffer, pH 6 with Vancomycine	—	41
		Ristocetin	—	41, 42
		Teicoplanin	—	41, 43
		0.1 M Phosphate and acetate buffer containing OM	—	44
		OG	—	45
Phenoxy acid derivatives	—	β-CD & TM-β-CD	—	39, 46
Polychlorinated biphenyls	—	0.1M CHES, pH 10, 2 M urea and 0.11 M SDS containing γ-CD	—	47
Silvex	—	0.4 M Borate, pH 10 containing Deoxy big CHAP	—	48

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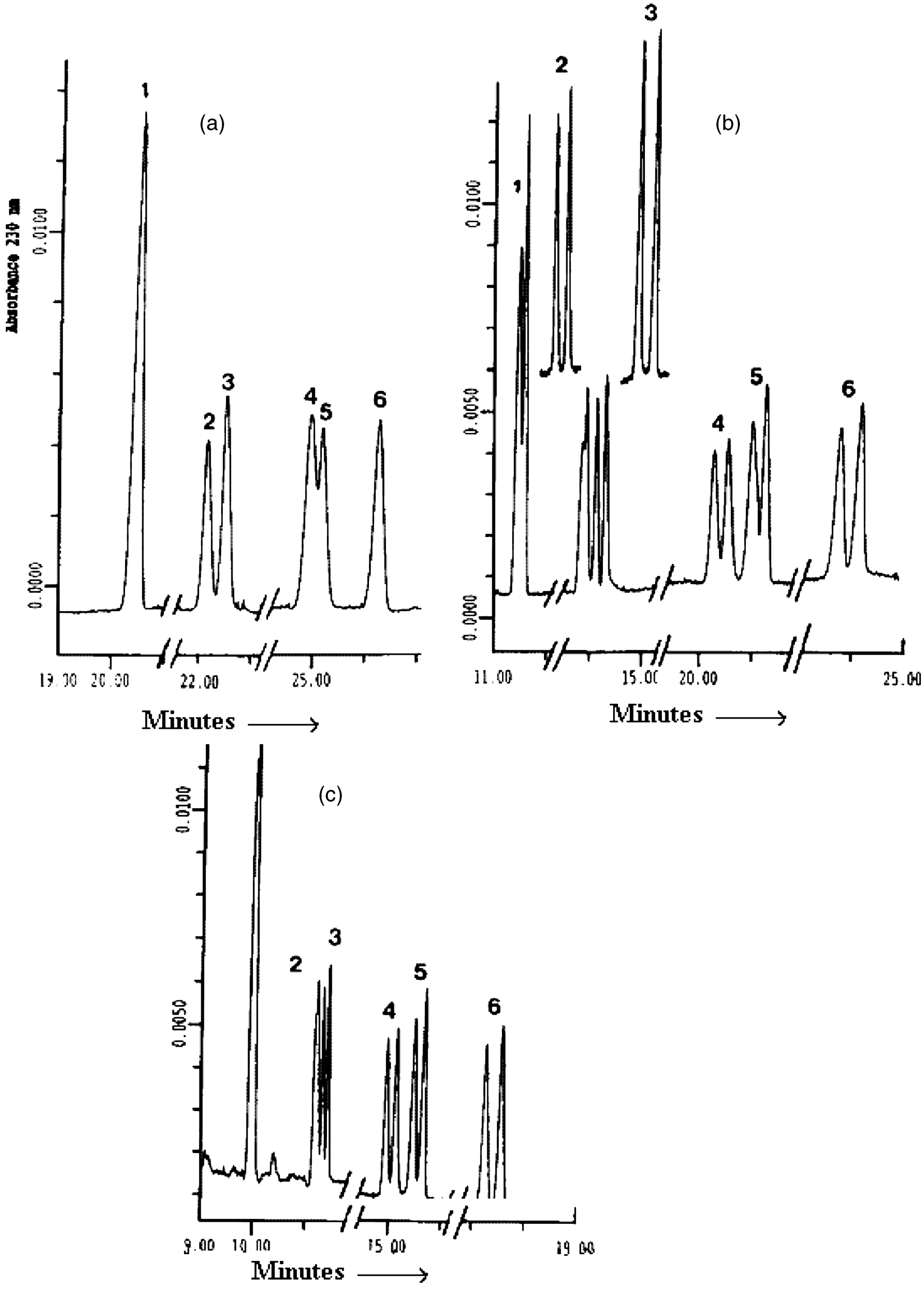

FIG. 1. Electropherograms of phenoxy acid herbicides using 175 mM sodium phosphate, pH 6.5, containing (a): 10 mM (b): 60 mM and (c): 100 mM n-octyl-β-D-maltopyranoside (OM), respectively, as BGEs with fused silica capillary (57 cm × 50 μm I.D.) and 25 kV as applied voltage. 1 = silvex, 2 = dichlorprop, 3 = mecoprop, 4 = 2,4-CPPA, 5 = 2,3-CPPA, 6 = 2,2-CPPA and 7 = 2-PPA (44).

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TABLE 3
The commonly used buffers with suitable pHs and wavelengths for the metal ion speciation in CE (50)

Buffers	pH	Wavelength (nm)
Phosphate	1.14–3.14	195
Citrate	3.06–5.40	260
Acetate	3.76–5.76	220
MES	5.15–7.15	230
PIPES	5.80–7.80	215
Phosphate	6.20–8.20	195
HEPES	6.55–8.55	230
Tricine	7.15–9.15	230
Tris	7.30–9.30	220
Borate	8.14–10.14	180
CHES	9.50–10.50	<190

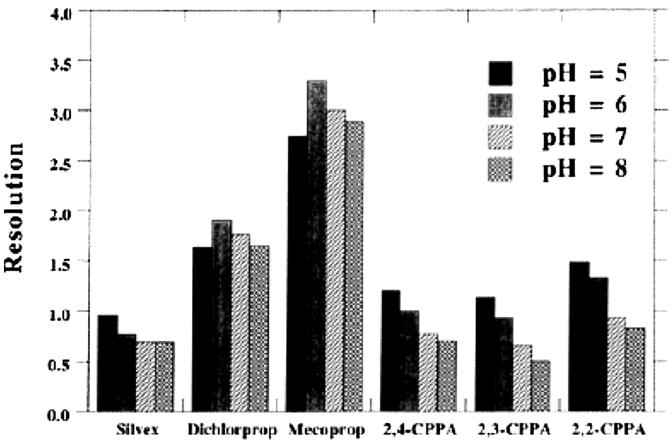

FIG. 2. The effect of pH on the chiral resolution of phenoxy acid herbicides using 100 mM sodium phosphate-sodium acetate buffers containing 60 mM OM as BGE. Other conditions as in Figure 1 (44).

diastereomeric complexes formed between enantiomers and the chiral selector. However, the increase in the buffer pH from 4 to 9 may result in an increase in the EOF and, therefore, by increasing the pH analysis time may be reduced. It is also important to note that the buffer pH may be altered in a secondary manner, i.e., by other parameters such as temperature, ion depletion, etc. The suitable range of pH of the various buffers is summarized in Table 3 (50). The literature reported herein indicates that a wide range of pHs were used for the chiral resolution of the environmental pollutants. Some reports indicate the chiral resolution was acidic while the other reports involved basic pHs, which clearly indicates that the need of the pH depends upon the type of the buffers used and other CE parameters. Generally, low pH is used to resolve cationic pollutants while high pH is required for the chiral resolution of anionic pollutants.

Crego and Marina (9) reviewed the chiral resolution of the environmental pollutants by CE and they reported the use of pH from 4.5 to 10.5. Weseloh et al. (25) studied the chiral resolution of biphenyls using phosphate buffer of different concentrations and 2.4 pH. Mechref and El Rassi (44) studied the effect of pH of the phosphate buffer on the chiral resolution of herbicides. The authors varied pH from 5 to 8 and the results are shown in Figure 2 and it may be concluded from this figure that pHs of 5 to 7 were found suitable for the chiral resolution. This is due to the ionic nature of the studied herbicides (silvex, dichlorprop, mecoprop, 2,4-CPPA, 2,3-CPPA and 2,2-CPPA) which interact with n-octyl-β-D-maltopyranoside (OM) surfactant used by the authors and hence the effect of pH on the chiral resolution was observed markedly. The same authors also resolved these herbicides using a mixture of phosphate and borate buffers of pH 5.0 (46). Recently, Tsunoi et al. (28) resolved phenoxy acid herbicides using phosphate and borate buffers of pH 9.0. Sarac et al. (26) reported 2.5 as the best pH of phosphate buffer for the chiral resolution of propionic acid derivatives. Therefore, the value of pH depends on the type of the chiral environmental pollutant, chiral selector and the buffer.

Ionic Strength of the BGE

The increasing ionic strength decreases the EOF and consequently an increase in the separation time occurs. Additionally, the increasing ionic strength also increases the current at a constant voltage to the point where adequate thermostating of the capillary becomes a concern. Besides, the increasing ionic strength decreases the diastereomers and wall interactions. Therefore, the selection of the ionic strength depends on several parameters such as capillary length and diameter, applied voltage and efficiency of the capillary thermostating condition. Besides, the ionic strength also provides the stability to diastereomers in some cases. It is very important to mention here that at high concentrations of buffers the excessive Joule heating occurs which has undesirable effect on the chiral resolution. Buffers problematic in this concern are those having electrolytes such as chloride, citrate and sulphate. However, the heating problem can be solved by decreasing the applied voltage, increasing length and decreasing internal diameter of the capillary. Therefore, the optimization of the chiral resolution of environmental pollutants may be achieved by varying the ionic strength of the BGE. Much work has not been carried out on the optimization of the chiral resolution by ionic strength variation. However, Mechref and El Rassi (46) studied the effect of ionic strength on the chiral resolution of herbicides varying the ionic strength from 50 to 200 mM and their findings are graphed in Figure 3. It may be seen from this figure that, generally, the resolution increased at higher ionic strength (200 mM). The authors described the best resolution at higher ionic strength due to the salting out effect, which is supposed to increase non-polar interactions with chiral micelles. The literature cited herein indicates that the ionic strengths of BGEs have been used for the chiral resolution.

TABLE 4
The chiral resolution of phenoxy acid herbicides using various cyclodextrins as the chiral selectors and derivatising agents (46)

Herbicides	α-CD	β-CD	γ-CD	DM- β-CD	HP- β-CD	TM- β-CD
Silvex						
Underivatized	0.00	0.39	0.00	0.00	0.10	3.03
Derivatized	0.00	2.54	2.43	0.00	0.20	0.85
Mecoprop						
Underivatized	0.80	0.15	0.00	1.44	0.57	2.49
Derivatized	0.29	0.00	0.53	0.45	0.00	7.04
Dichlorprop						
Underivatized	0.67	0.00	0.00	0.00	0.75	1.05
Derivatized	0.14	0.00	0.00	0.00	0.00	3.76
2,4-CPPA						
Underivatized	0.43	1.00	0.00	0.00	0.35	1.08
Derivatized	0.00	3.43	0.00	1.28	2.45	0.20
2,3-CPPA						
Underivatized	0.27	1.68	0.00	0.00	1.00	0.00
Derivatized	2.63	3.33	0.00	1.28	2.45	0.20
2,2-CPPA						
Underivatized	0.00	0.00	0.00	0.00	0.00	0.00
Derivatized	0.00	0.00	0.00	0.79	1.29	1.76
2-PPA						
Underivatized	0.00	0.00	0.00	0.00	0.00	0.00
Derivatized	0.00	5.68	0.00	1.89	1.39	0.00

DM-β-CD: 2,6-di-O-methyl-β-cyclodextrin; HP-β-CD: hydroxypropyl-β-cyclodextrin; TM-β-CD: 2,3,6-tri-O-methyl-β-cyclodextrin; 2,2-CPPA: 2-(2-chlorophenoxy) propionic acid; 2,3-CPPA: 2-(3-chlorophenoxy) propionic acid; 2,4-CPPA: 2-(4-chlorophenoxy) propionic acid; and 2-PPA: 2-phenoxypropionic acid.

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Structures and Types of the Chiral Selectors

Mostly the chiral resolution of the environmental pollutants was carried out using these chiral selectors in the BGE. The chiral selectors are supposed to interact with the enantiomers of the environmental pollutants, which will be discussed later in the detail in mechanisms part of this review. Therefore, the selection of the suitable chiral selectors for a specific chiral environmental pollutant is the key parameter. The selection of the chiral selector is designed by considering the interaction sites of the chiral selector and the environmental pollutants. The knowledge of the basic chemistry is helpful to select the suitable chiral selector. The most commonlly used chiral selectors in CE are given in Table 1. Of course many of the compounds have been used as the chiral selectors (Table 1) but the use of cyclodextrins (CDs) is very common, which is due to the good tendency of the distereomeric complexes formation of these chiral selectors. Besides, the good solubility in aqueous buffers and inexpensive nature make these chiral selectors as the best choice in CE. CDs occur in α-, β- and γ- forms and their derivatives. Mechref and El Rassi (46) used α-, β- and γ-CDs and their derivatives for the chiral resolution of phenoxy acid herbicides. The chiral resolution of these herbicides is given in Table 4, which indicates 2,3,6-tri-O-methyl-β-CD as the best chiral selector. Furthermore, these authors also studied the effect of the concentrations of these CDs on the enantiomeric resolution of the environmental pollutants. The concentrations of these CDs were varied from 5 to 30 mM and the results are shown in Figure 4, which indicates an increase in resolution using the higher concentration of

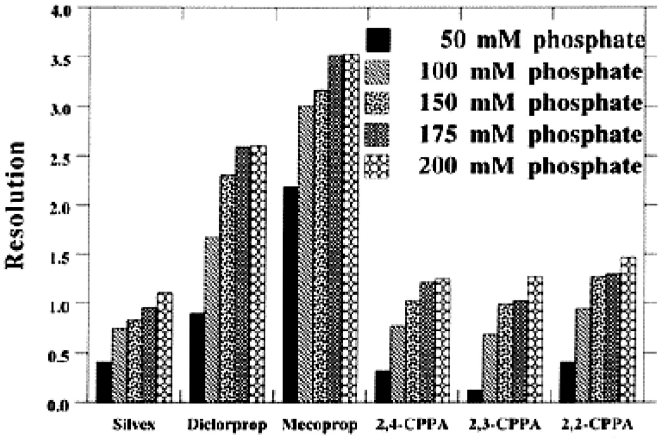

FIG. 3. The effect of ionic strength on the chiral resolution of phenoxy acid herbicides using sodium phosphate buffer containing 60 mM OM as BGE. Other conditions as in Figure 1 (44).

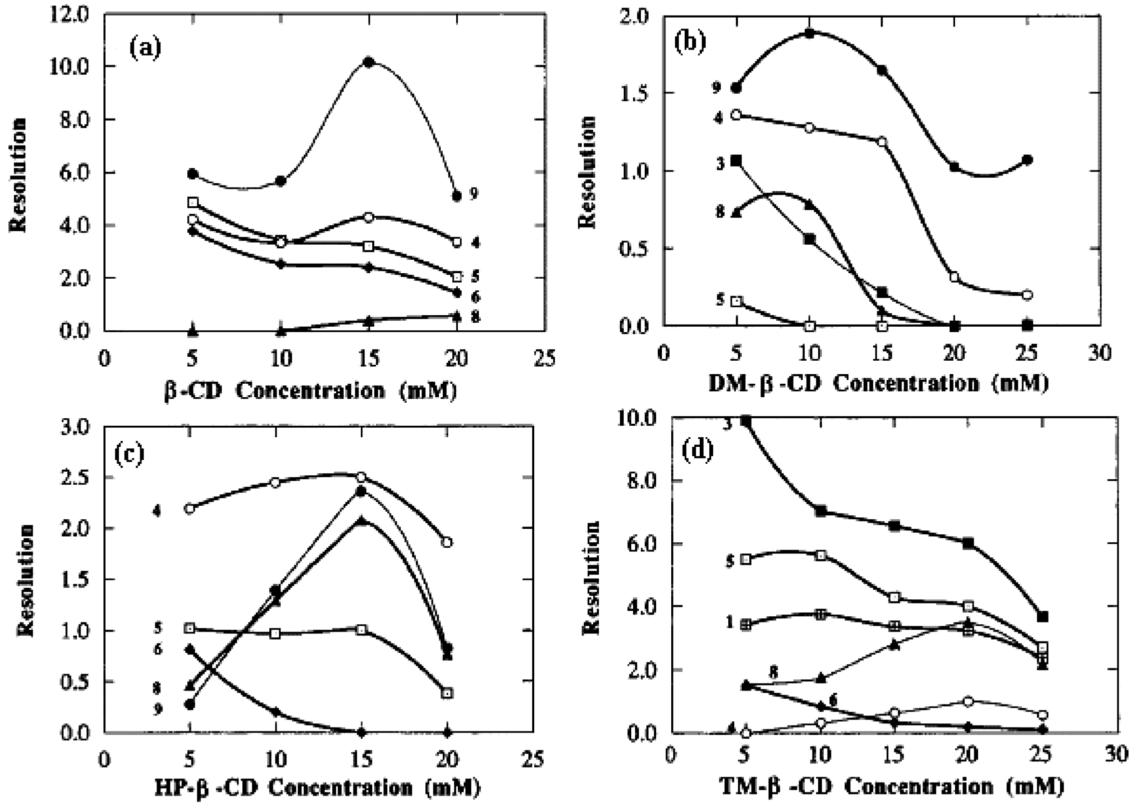

FIG. 4. The effect of the concentrations of cyclodextrins on the chiral resolution of phenoxy acid herbicides using 25 mM sodium phosphate and 600 mM borate buffers (pH 5.0) containing different concentrations of (a): β-CD, (b): DM-β-CD, (c): HP-β-CD and (d): TM-β-CD as BGEs. 1 = dichlorprop, 3 = mecoprop, 4 = 2,3-CPPA, 5 = 2,4-CPPA, 6 = silvex, 8 = 2,2-CPPA, 9 = 2-PPA (46).

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β-CD and HP-β-CD while the resolution decreased at higher concentrations of DM-β-CD and TM-β-CD. These different trends of the chiral resolution of these CDs may be because of some interactions such as steric effect, etc. at higher concentrations.

Applied Voltage

The applied voltage is one of the most important aspects to optimize the chiral resolution of the environmental pollutants by CE. In general, the increasing of voltage results in an increase of EOF, short migration time, sharp peaks and, sometimes, the improved resolution. Therefore, it is advisable to start with a moderate value of voltage, i.e., between 10 to 15 kV. Increasing voltage has a number of disadvantages also. If the sample matrix ionic strength is much greater than the EOF the increased production of Joule heat can not be efficiently dissipated. Additionally, the heating of the capillary results in a decreased solution viscosity and hence the reproducibility is lost. The non-reproducibility is observed due to an increase into the ionic mobility and pollutant diffusion. The magnitude of the applied voltage also depends on the type of buffer used. Nelson et al. (51) reported no heating of the capillary up to 30 kV as the applied voltage when borate buffer was used while heating of the capillary was observed even at 10 and 12 kV using CAPS and phosphate buffers respectively. As per the Crego and Marina review 20 to 30 kV have been used as the applied voltage with acetate buffer.

Temperature

Generally, at high temperature the viscosity of the BGE increases which results in the short analysis time and poor resolution. Also, it is important to note that when sample introduction is hydrostatic the sample volume increases at higher temperature, which sometimes results in poor resolution. Besides, concurrent changes in buffer pH and peak broadening also occurs. Contrarily, some of the advantages have also been observed at elevated experimental temperatures. Briefly, temperature effects the chiral resolution but it has not been used as the routine optimization parameter as the control of temperature is difficult in the present model of CE. However, Mechref and El Rassi (44) studied the effect of temperature on the chiral resolution of herbicides and the results are shown in Figure 5, which indicates that the chiral resolution improved at lower temperature.

Structures of the Chiral Pollutants

The chiral resolution by CE depends on the formation of diastereomers complexes and, therefore, structures and sizes of the

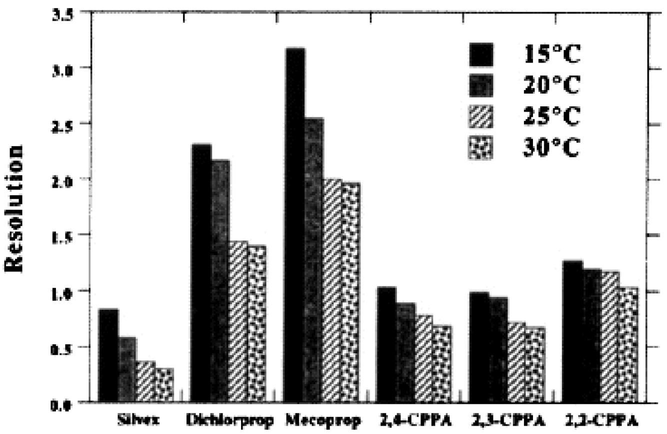

FIG. 5. The effect of the temperature on the chiral resolution of phenoxy acid herbicides using 150 mM sodium phosphate buffer (pH 6.5) containing 60 mM OM as BGE. Other conditions as in Figure 1 (44).

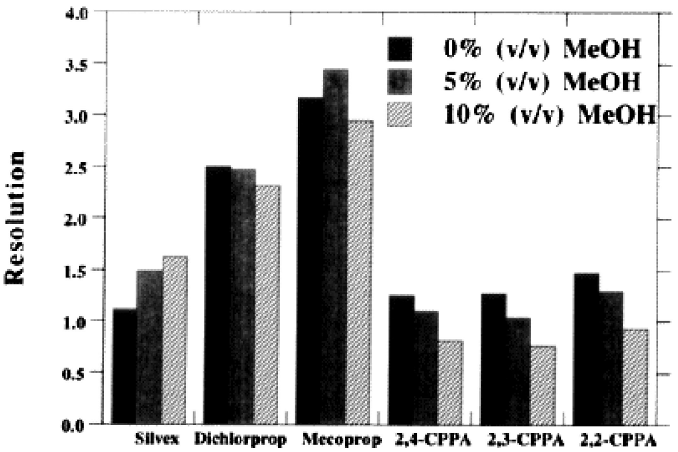

FIG. 6. The effect of methanol concentration on the chiral resolution of phenoxy acid herbicides using 200 mM sodium phosphate-sodium acetate buffers (pH 6.5) containing 60 mM OM as BGE. Other conditions as in Figure 1 (44).

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pollutants are also crucial for their chiral resolution. To study this aspect, phenoxy acid herbicides, i.e., herbicides listed in Table 4, may be considered as the best class of the chiral pollutants. Mechref and El Rassi (44) studied these herbicides using CDs as the chiral selectors. It has been reported that the chiral resolution of these herbicides was in the order of 2-PPA > 2,2-CPPA > 2,3-CPPA. 2-PPA does not has any chlorine atom on the phenyl ring while 2,2-CPPA and 2,3-CPPA contain chlorine atoms on the *ortho*- and *meta*- positions separately and respectively. Therefore, it may be concluded that the chlorine atom is creating some sort of hindrance in the diastereomeric complex formation. Furthermore, it may be observed that the *ortho*-position is creating greater strain in comparison to the *meta*- position. Briefly, the steric effect, due to the presence of chlorine atoms, is playing a dominant role in the chiral resolution of these herbicides. Similarly, the different pattern of the chiral resolution of the environmental pollutants may be correlated with their structures. Finally, the optimization of the chiral resolution of environmental pollutants may be achieved by considering their structures and using the appropriate CE conditions.

Organic Modifiers

Generally, buffers of different concentrations and pHs are used as the BGEs for the chiral resolution of the pollutants by CE. However, the use of some organic solvents called organic modifiers may be useful for the optimization of the chiral resolution. The addition of the organic modifiers may change the EOF, the formation of diastereomeric complexes and their interactions with the capillary wall, cause a decrease in conductivity and thermal diffusion etc. Therefore, the chiral resolution may be optimized varying the concentrations and the types of the organic modifiers. The most important organic modifiers are acetonitrile, methanol, ethanol, 1,4-diaminobutane, etc. Care should be taken to adjust the concentration of these organic modifiers as their higher concentration may precipitate the buffer constituents, which may block the capillary. Mechref and El Rassi (44) studied the effect of the concentration of methanol on the chiral resolution of herbicides. The authors used 5 and 10% methanol concentrations in the phosphate and acetate buffer mixture and the results are shown in Figure 6. It may be concluded from this figure that 5% methanol resulted into the best resolution.

Other Parameters

Besides the parameters discussed above, some other factors can also be used to optimize the chiral resolution by CE. These parameters include the reversal of polarity, volume of the sample injected, use of the EOF modifiers and pre-derivatization of the chiral pollutants with a suitable chiral selector. In a normal CE machine the anode (+) is always at the inlet and the cathode (−) at the outlet ends. In this format, EOF is towards the cathode (detector). If set in reverse polarity, the direction of EOF is away from the detector and hence only negatively charged diastereomeric complexes with electrophoretic mobility greater than the EOF will pass the detector. This format is typically used with capillaries that are coated with substances that reverse the net charge of the inner wall (reverse EOF), or when diastereomeric complexes are all net negatively charged. Sometimes, partial resolution of the chiral pollutants is observed due to the sample over-loading. Under such circumstances, the maximum resolution can be achieved by reducing the sample volume or decreasing the concentration of the pollutants. Mechref and El Rassi (46) derivatized phenoxy herbicides with CDs and resolved them without CD in BGE and the resolution was compared with the resolution obtained when using CD in BGE and the authors reported different patterns of the chiral resolution (Table 4) using these approaches better resolution of some pesticides only (Table 4). Besides, the chiral resolution may be

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optimized by coating the capillary wall with the suitable coating agent such as polyacrylamide, alkylhydroxyalkyl cellulose, polyvinyl alcohol, tetra-alkyl ammonium ion, etc. Additionally, the variation in the length and diameter of the capillary may be used to optimize the chiral resolution.

Sometimes, the optimization of the chiral resolution in CE is optimized by adding some surfactants (at a concentration above its critical micellar concentration). The improvement in the chiral resolution occurred due to the formation of micellar. The mechanisms of the chiral resolution slightly changed towards the chromatographic behavior and, therefore, this modality of CE is called micellar electrokinetic chromatography (MEKC). A surfactant is a molecule possessing two zones of different polarity and results in the solutions of special characteristics. The surfactants are divided into three categories, i.e., ionic (cationic and anionic), non-ionic and zwitterionic. The surfactant molecules form micelle and the partition of the diastereomeric complexes occurred between this micelle and BGE. Mechref and El Rassi (44) studied the effect of the different concentrations of n-octyl-β-D-maltopyranoside (OM) as the surfactant. The authors used 30 to 100 mM concentrations of the surfactant (Figure 7). Figure 7 clearly indicates that 60 mM concentration is the best for the chiral resolution of the reported herbicides. The authors also reported the decrease in EOF with the increasing concentration of OM and the decrease was more pronounced for the more hydrophobic pollutant, i.e., silvex. According to authors, OM form a palaside layer of the micelle in which the herbicides are likely to be solubilized and hence favor the diastereomeric complex formation, which results in the maximum resolution.

OPTIMIZATION BY DEPENDENT VARIABLES

As mentioned earlier, there are certain parameters, i.e., field strength (V/m), EOF, Joule heating, BGE viscosity, sample diffusion, sample mobility, sample charge, sample size and shape, sample interaction with capillary and BGE, molar absorptivity, etc. which also contribute towards the chiral resolution of the pollutants. It is very interesting to note that these parameters can not be controlled directly. However, the variation in the variable parameters can be carried out through the independent variables. For instance, the optimization of the chiral resolution of the pollutants may be achieved by changing the temperature of the capillary, which may result in the decrease of viscosity, increase in EOF, etc. Based on experience, a variation in the independent parameters may be useful to control the optimization of the chiral resolution of pollutants via dependent variables. A method development for the chiral resolution of the environmental pollutants is presented in Scheme 1. First of all, the CE parameters are selected and set on the CE machine and then the experiment is started and, finally, the chiral resolution is optimized by varying the above-mentioned parameters. The chiral resolution is expressed in the form of separation and resolution factors as in chromatography which are calculated from ectropherograms (peaks).

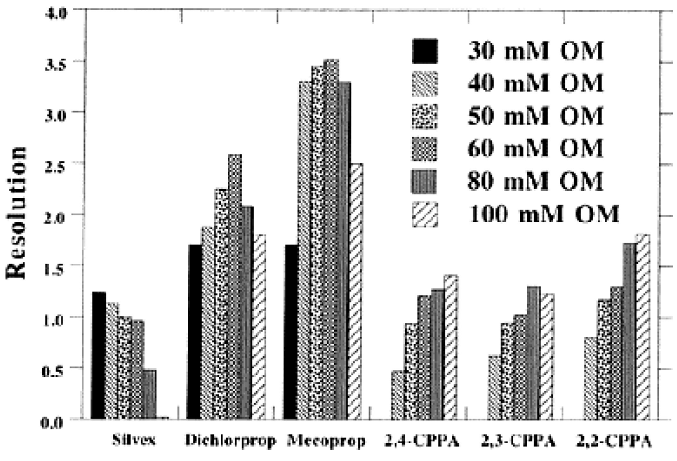

FIG. 7. The effect of the concentration of OM on the chiral resolution of phenoxy acid herbicides using 175 mM sodium phosphate buffer (pH 6.5) as BGE. Other conditions as in Figure 1 (44).

DETECTION

Generally, the chiral pollutants in the environment occur at low concentrations and, therefore, a sensitive detection is very important and required in chiral CE. The most common detectors used in the chiral CE are UV, electrochemical, fluorescence and mass spectrometer. Mostly, the detection of the chiral resolution of drugs and pharmaceuticals in CE has been achieved by UV mode. Similarly, the detection of the chiral pollutants in CE has been achieved by UV detector in some reports (9, 27, 44, 46). The selection of the UV wavelength depends on the type of buffer, chiral selector and the environmental pollutants. The suitable wavelengths for the different buffers are given in Table 5. However, the concentration and the sensitivity of UV detection are restricted in so far as the capillary diameter limits the optical path length. It has been observed that some

TABLE 5
The commonly used buffers with suitable pHs and wavelengths for the chiral resolution of the pollutants in CE (50)

Buffers	pH	Wavelength (nm)
Phosphate	1.14–3.14	195
Citrate	3.06–5.40	260
Acetate	3.76–5.76	220
MES	5.15–7.15	230
PIPES	5.80–7.80	215
Phosphate	6.20–8.20	195
HEPES	6.55–8.55	230
Tricine	7.15–9.15	230
Tris	7.30–9.30	220
Borate	8.14–10.14	180
CHES	9.50–10.50	<190

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pollutants, especially organochloro pesticides, are not very UV sensitive and, therefore, for such type of applications electrochemical, mass spectrometer, etc. are the best detectors. Some of the chiral selectors such as proteins and macrocyclic glycopeptide antibiotics are UV sensitive and hence the detection becomes poor.

Only few reports are available in the literature dealing with the limits of the detection for the chiral resolution of the pollutants by CE, which indicate mg/L to μg/L as the limits of the detection. Tsunoi et al. (28) carried out an extensive study on the determination of the limits of the detection for the chiral resolution of herbicides. The authors used 230 nm wavelength for the detection and the minimum limit of the detection achieved was 4.7×10^{-3} M for 2,4-dichlrophenoxy acetic acid. On the other hand, Mechref and El Rassi (46) reported better detection limits, for herbicides, in the derivatized mode of the chiral resolution in comparison to the underivatized mode. For example, the limit of the detection was enhanced by almost an order of magnitude from 1×10^{-4} M (10 pmol) to 3×10^{-5} M (0.36 pmol) in UV mode. In the same study, the authors reported 2.5×10^{-6} and 1×10^{-9} M as the limits of the detection for the herbicides by fluorescence and laser-induced fluorescence detectors, respectively.

SAMPLE TREATMENT

The chiral resolution is very sensitive and the presence of any foreign impurity may affect it. It is very common and natural for many of the constituents to be present in the sample of the chiral pollutant collected from the environment. Therefore, the sample pre-treatment is a very important and necessary step for the reproducible chiral resolution. Real samples often require the application of simple procedures such as filtration, extraction, dilution, etc. A search of literature conducted and discussed herein (Table 2) indicated that all of the chiral resolution of the environmental pollutants was carried out, by CE, in the laboratory synthesized samples only. Therefore, no report is published on the sample (natural sample) pre-treatment for the chiral resolution of the environmental pollutants by CE. However, pre-treatment of various biological samples was reported before the chiral resolution of drugs and pharmaceuticals. Besides, some of the reviews have also been published on the pre-treatment and sample preparation methodologies for the simple analysis of pollutants (52–55). Therefore, these approaches may be utilized for the pre-concentration and sample preparation in chiral CE of the environmental pollutants. Ezzell et al. (52) used the solvent extraction procedure for the extraction of the organophosphorus pesticides from the soil sample at the μg/kg level. The outline of the apparatus they used is shown in Figure 8. On the other hand, Majors (53) described the sample preparation for the environmental analysis using solid phase extraction, supercritical fluid extraction, micro-solvent extraction, microwave-assisted and accelerated solvent extraction, liquid-liquid electro-extraction, selective extraction based on molecular recognition, supported liquid membranes, microdialysis and chromatography. Dabek-Zlotorzynska et al. (55) also reviewed the sample pre-treatment methodologies for the environmental analysis before CE. The authors also described the above-mentioned methods as ways to pre-treat the sample. Besides, some reviews have also appeared in last few years on this issue (56–58). Whang and Pawliszyn (59) designed an interface that enables the solid phase micro-extraction (SPME) fiber to be inserted directly into the injection end of a CE capillary. They prepared a semi- “custom made” polyacrylate fiber to reach the SPME-CE interface (Figure 9). The authors tested the developed interface to analyze phenols in water and, therefore, the same may be used for the chiral resolution of the pollutants.

VALIDATION OF THE METHODS

CE is growing as the fast, efficient and versatile technique for the chiral resolution of drugs, pharmaceuticals and pollutants

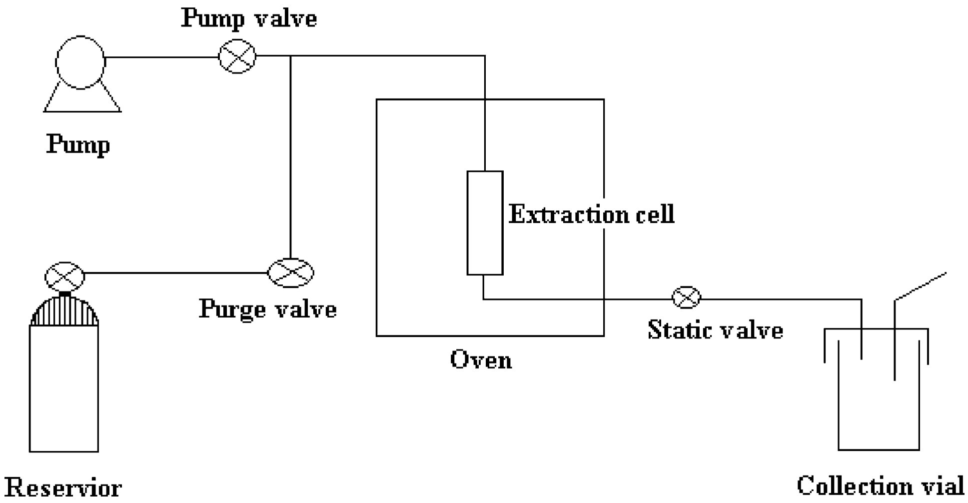

FIG. 8. Schematic diagram of the accelerated solvent extraction system (52).

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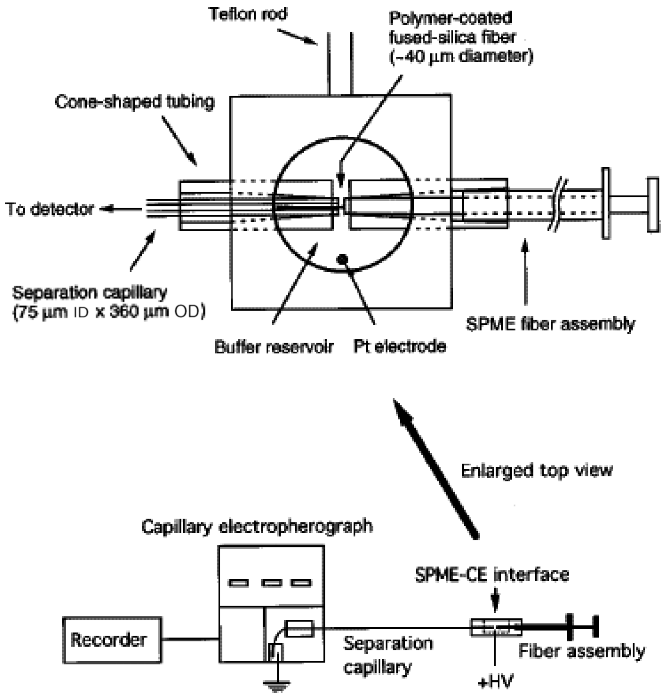

FIG. 9. Schematic diagram of the solid phase micro extraction capillary electrophoresis (SPME-CE) system (59).

but still requires improvements in its working conditions to get reproducibility. To the best of our knowledge, very few works, even of simple analysis of the pollutants, which used CE in routine practice, have been used (55). Therefore, in the present time, more emphasis is required on the method validation. For routine analysis it is essential to keep the migration times constant in order to allow automatic peak identification by means of commercial data analysis software. Automatic peak identification and quantification are only possible if the relative standard deviation of migration times is less than 0.5% (60). Several reviews have been published which describe the improvement in the reproducibility of the results (60–66).

Another approach for the qualitative and quantitative reproducibilties is the transformation of the total time x-scale of electrophoretic data into the corresponding effective mobility scale (μ-scale) (67, 68). The conversion leads to a better interpretation of the obtained electropherograms in terms of separation, and enables better direct comparison of the electropherograms and easier peak tracking when trying to identify single components from complex matrices, specially when UV visible signatures of the components are also available (68). According to authors, a quantitative improvement was achieved in the μ-scale with significantly better peak area precision which equates to better precision in quantitative analysis than with the primary time scale integration. However, electrophoretic-based data processing CE software is needed to be able to handle the electrophoretic data directly.

Therefore, it may be assumed that the selectivity of different environmental pollutants by CE is quite good. However, the reproducibility is still a problem in CE. Therefore, many attempts have been made to solve this problem. Organic solvents have been added into BGE to improve the reproducibility of many of the pollutants. It has also been reported that the organic solvents ameliorate the solubility of the hydrophobic complexes, reduce their adsorption onto the capillary wall, regulate the distribution of diastereomeric complexes between aqueous phase and micellar phase, adjust the viscosity of the separation medium, and accordingly accomplish the improvement in reproducibility. The constant pH of the electrolyte solution is very important from the selectivity and reproducibility points of view. The pH controls the behavior of EOF, acid/base dissociation equilibria of complexes and the state of the existing complex. Therefore, the selectivity and reproducibility can be improved by adjusting pH of the BGE.

MECHANISMS OF THE CHIRAL RESOLUTION

It is a well known fact that the chiral environment is essential for the enantiomeric resolution by any technique. In CE the chiral situation is provided by the chiral compound used in BGE and is called the chiral selector or chiral BGE additive. Basically, the chiral recognition mechanisms in CE are similar to those in chromatography using chiral mobile phase additives. The chiral resolution occurred due to the formation of diastereomeric complexes between the enantiomers of the pollutants and the chiral selector. The formation of diastereomeric complexes depends on the type and nature of the chiral selector used and the pollutants.

In the case of CDs the inclusion complexes are formed and the formation of diastereomeric complexes is controlled by a number of interactions such as π-π complexation, hydrogen bondings, dipole-dipole interactions, ionic bindings and steric effects. Zerbinati et al. (31) used ethylcarbonate-β-CD, hydroxypropyl-β-CD and native α-CD for the chiral resolution of mecoprop and dichlorprop. The authors calculated the performances of these chiral selectors by means of two-levels full factorial design and the calculating inclusion constants from CE migration time data. Furthermore, they have proposed the possible structure of inclusion complexes on the basis of molecular mechanics simulations. Recently, Chankvetadze et al. (69) explained the chiral recognition mechanisms in CD-based CE using UV, NMR and electrospray ionization mass spectrometric methods. Furthermore, the authors determined the structures of the distereomeric complexes by X-ray crystallographic method.

The macrocyclic antibiotics have both similarities and differences with the CDs. Most of the macrocyclic antibiotics contain ionizable groups and, consequently, their charge and possibly their three-dimensional conformation can vary with the pH of the BGE. The complex structures of the antibiotics containing different chiral centers, inclusion cavities, phenyl rings, pyranose, furanose, quinoline and thiazole rings, bridges, several hydrogen donor and acceptor sites, sugar moieties, and other groups are responsible for their surprising chiral selectivities.

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This allows for an excellent potential to resolve a greater variety of racemates. The possible interactions involved in the formation of diastereomeric complexes are π-π complexation, hydrogen bonding, inclusion complexation, dipole interactions, steric interactions and anionic and cationic bindings . Similarly, the diastereomeric complexes are formed with other chiral selectors involving specific interactions. In this way, the diastereomeric complexes possessing different physical and chemical properties separated on the capillary path (achiral phase). The different migration times of these formed diastereomeric complexes depend on their sizes, charges and interaction with the capillary wall and as a result these complexes eluted at different time intervals.

CE VS. HPLC

Nowadays, HPLC is supposed as the method of choice for the chiral resolution of a wide range of racemic compounds including drugs, pharmaceuticals, agrochemicals and the environmental pollutants. The wide application of HPLC is because of the development of various chiral stationary phases and reproducibility. However, HPLC suffers from certain drawbacks as the chiral selectors are fixed on the stationary phase and hence no variation in the concentrations of the chiral selectors can be carried out. Besides, a large amount of the costly solvents is consumed to establish the chiral resolution procedure. Additionally, the poor efficiency in HPLC is due to the profile of the laminar flow, mass transfer term and possible additional interactions of enantiomers with the residual silanol groups of the stationary phase.

Contrarily, CE is the newly developed technique having no chiral stationary phase. The chiral resolution in CE is achieved using the chiral selectors in the BGE. The chiral resolution in CE is very sensitive involving the use of inexpensive buffers. Besides, the high efficiency of CE is due to the flat profile originated and to a homogeneous partition of the chiral selector in the electrolyte, which in turn, minimizes the mass transfer. Generally, the theoretical plate number in CE is higher in comparison to HPLC and, therefore, a good resolution is achieved in CE. Besides, more than one chiral selector can be used simultaneously for getting the best resolution. However, the reproducibility is the major problem in CE and, therefore, the technique is not popular for routine chiral resolution. The other drawbacks of CE include the waste of the chiral selector as it is used in BGE. Besides, chiroptical detectors such as polarimetric and circular dichroism can not be used as the detection device due to the presence of the chiral selector in the BGE. Moreover, some of the well known chiral selectors may not be soluble in the BGE and, thus, a stationary bed of a chiral selector may be allowed to transfer the advantages of a stationary bed inherent to HPLC to an electrically driven technique, i.e., CE. This will allow CE to be coupled with mass spectrometer, polarimeter, circular dichroism and UV detectors with out any problem. Briefly, at present the CE is not a better technique than HPLC for the chiral resolution due to reproducibility problems but, of course, it has a bright future.

CONCLUSION

The chiral resolution of the environmental pollutants at a trace level is a very important and challenging issue nowadays. Gas chromatography and HPLC have been used for the chiral resolution of the environmental pollutants but, in recent years, CE has also been used for this purpose. A search of literature indicates a few reports on the chiral resolution of environmental pollutants by CE but it could not achieve a place in the routine chiral analysis of these pollutants due to its poor reproducibility and the limit of the detection. Therefore, many of the workers have suggested different modifications and alternatives to make the CE a method of choice. To get the good reproducibility, the selection of the capillary wall chemistry, pH and ionic strength of the BGE, chiral selectors, detectors and optimization of BGE have been described and suggested (70–76).

Apart from the above-discussed-points for the improvement of CE applications for the chiral resolution, some other aspects should also be addressed so that CE can be used as the routine method in this field. The important points relating to this include the development of the new chiral selectors and detector devices. The non-reproducibility of the methods may be due to the heating of BGE after a long run of CE machine. Therefore, to keep the temperature constant throughout the experiments, a cooling device should be included in the machine. There are only a few reports dealing with the method validation. To make the developed method more applicable the validation of the methodology should be determined. The chiral capillaries should be developed and the CE machine should be coupled with mass spectrometer, polarimetric and circular dichroism detectors, which might result in good reproducibility and low limits of detection. All the capabilities and possibilities of CE as the chiral resolution technique have not been explored and are currently underway. However, CE will be realized as a widely recognized method of choice for the chiral resolution of the environmental pollutants. In summary, there are many developments necessary for the advancement of CE for the chiral resolution of environmental pollutants. Definitely, CE will prove itself as the best technique for chiral resolution of the environmental pollutants within the next few years and will become the technique of routine analysis in most of the environmental laboratories.

ABBREVIATIONS

BGE	Back ground electrolyte
CD	Cyclodextrin
CE	Capillary electrophoresis
CHES	2-(*N*-Cyclohexylamino) ethansulfonic acid
2,2-CPPA	2-(2-Chlorophenoxy) propionic acid
2,3-CPPA	2-(3-Chlorophenoxy) propionic acid
2,4-CPPA	2-(4-Chlorophenoxy) propionic acid
2,4-D	(2,4-Dichlorophenoxy) acetic acid
DCPP	2-(2,4-Dichlorophenoxy) propionic acid
EOF	Electroosmotic flow
ESI	Electron spray ionization

GC	Gas chromatography
HEPES	N-Hydroxyethyl plperazine ethanesulfonlc acid
HPLC	High performance liquid chromatography
ICP	Inductively coupled plasma
MCPP	2-(4-Chlorophenoxy) propionic acid
MEKC	Micellar electrokinetic chromatography
MES	2-(*N*-Morpholino) ethansulfonic acid
MS	Mass spectrometer
NMR	Nuclear magnetic resonance
OG	n-Octyl-β-D-glucopyranoside
OM	n-Octyl-β-D-maltopyranoside
2-PPA	2-Phenoxypropionic acid
SDS	Sodium dodecyl sulphate
SPME	Solid phase micro extraction
SPME-CE	Solid phase micro extraction capillary electrophoresis
2,4,5-T	(2,4,5-Trichlorophenoxy) acetic acid
TM-β-CD	2,3,6-Tri-*O*-methyl-β-cyclodextrin
UV	Ultraviolet

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