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RECENT ADVANCES ON THE USE OF CYCLODEXTRINS IN THE CHIRAL ANALYSIS OF DRUGS BY CAPILLARY ELECTROPHORESIS

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Highlights

- The potential of CDs in the CE resolution of drug enantiomers is described
- Enantioseparation mechanisms for chiral drugs in CE with CDs are studied
- Applications of the developed chiral analytical CE methods using CDs are presented ~~Applications of CE with CDs to the chiral analysis of drugs: quantitative analysis, enantiomeric purity, stability studies, biological samples, metabolism studies, criminalistics and forensic investigations.~~

Abstract

The most recent advances on the use of cyclodextrins as chiral selectors in capillary electrophoresis for the enantioseparation of drugs are reviewed in this article. The types of cyclodextrins employed and the resolutions achieved are discussed. The use of dual chiral systems, modified capillaries, non-aqueous media or microfluidic devices is also included and the mechanisms for enantioseparation of drugs and the inversion of the enantiomer migration order are studied. The most relevant applications developed to carry out the quantitation of chiral drugs, to assess the enantiomeric purity of pharmaceutical formulations, to study their metabolism or to achieve criminalistic or forensic investigations are described. Articles published in the last six years (period from 2010 to 2015) are considered.

Key words: chiral, capillary electrophoresis, cyclodextrins, drugs, analysis, enantiomer.

1. Introduction

The determination of the enantiomers of chiral drugs is of crucial importance in pharmaceutical analysis since one of the enantiomers can be active from a pharmacological point of view, while the other (s) can be inactive, have a different biological activity or even be toxic. Moreover, the

increasing use of drugs marketed as pure enantiomers requires the control of the enantiomeric impurities using potent and sensitive analytical techniques.

Capillary Electrophoresis (CE) is a powerful technique for chiral analysis [1-4]. Among the advantages of CE, its simplicity, high efficiency, versatility, rapid analysis, high-resolution power, small sample volume required and low operating costs can be cited. Moreover, coupling of CE with mass spectrometry detection confers to CE a high sensitivity together with the possibility of unequivocal identification of drugs or their impurities or metabolites in a variety of complex matrices such as pharmaceutical formulations or biological samples.

Most chiral separations by CE are carried out by adding a chiral selector to the separation buffer [5]. The chiral selector forms a complex with both enantiomers, giving rise to differences in the electrophoretic mobility between them. Cyclodextrins (CDs), crown ethers, proteins, surfactants, macrocyclic antibiotics, ligand-exchange complexes and polysaccharides are important types of chiral selectors used in chiral CE. Among all types of chiral selectors described in the literature, CDs are the most frequently employed [6].

CDs are cyclic oligosaccarides that consist of (α-1,4)-linked α-D-glucopyranose units. α-, β- and γ-CDs contain six, seven and eight glucose units, respectively, and form a ring with a truncated cone shape. CDs form inclusion complexes with the enantiomers whose stability depends on the molecular properties of the enantiomer and the CD. The variety in the diameter of the cavity and the substituents in the CD provide the possibility of enantioseparations of many chiral compounds with different size and functional groups using uncharged, positively and negatively charged CD derivatives [7, 8]. Moreover, the high solubility of CDs in aqueous media and their low UV absorbance are advantages to be employed in CE [9]. In fact, native and derivatized CDs have been used to achieve the enantioseparation of a wide variety of chiral drugs by CE.

In this article, the main developments and applications of chiral CE with CDs in pharmaceutical analysis that have taken place during the last six years are reviewed. Articles published in the period of time from 2010 to 2015 have been considered. In the course of these years, some review articles dealing with specific subjects of the use of chiral CE in pharmaceutical analysis have been published. In particular, the enantioseparation of drugs with multiple chiral centers [10], the use of non-aqueous capillary electrophoresis (NACE) [11], the application of antibiotics as chiral selectors [12, 13], and the enantioseparation of fluoroquinolones drugs [14] have been reviewed.

2. Types of CDs used in the enantioseparation of drugs

Table 1 shows the types of CDs employed to achieve the enantiomeric separation of compounds of pharmacological interest. In general terms, the best enantiomeric separations were obtained with anionic CDs [15-26] probably because the anionic CD derivatives migrate toward the anode against the EOF which increases the migration time giving rise to more opportunities to the interaction between the analyte and the CD improving the enantioresolution. The enantioseparation of positively charged basic drugs is further improved with anionic CD derivatives due to: i) the opposite charge which increases the affinity between the enantiomers and the CD, and ii) the opposite electrophoretic mobility of the enantiomers and the CD. Nevertheless, sometimes neutral CDs gave better separations than anionic ones [27-31]. It can be observed in Table 1 that anionic β-CD derivatives have been the most commonly used CDs for the enantioseparation of drugs, probably because the size of their cavity fits better to the size of the majority of drugs. Nevertheless, the cavity may not fit the size of the drug but rather just ionic interactions without inclusion complex formation may yield the separation.

The resolution (Rs) values obtained for the compounds separated with each CD employed in the reviewed period are also grouped in Table 1. When the numerical values of R_s are not given in the original article, it is indicated in the table if the enantiomeric separation was possible (R) or not (NR). It can be observed that β-CD, carboxymethyl-β-CD (CM-β-CD), hydroxypropyl-β-CD (HP-β-CD), highly sulfated-γ-CD (HS-γ-CD) and sulfated-β-CD (S-β-CD) were the most employed CDs for the enantiomeric separation of chiral drugs by CE. In order to compare the results obtained with neutral and anionic β-CDs, Table 2 shows the best enantioresolution achieved for a group of drugs with both types of CDs. For some compounds such as 1-(4-methoxyphenyl)-2-(methylamine)-ethanol, 2-amino-1-phenyl-ethanol, atenolol, butylone, cetirizine, chloroquine, mefloquine, mephedrone, methoxytolterodine, metoprolol, naphyrone, ofloxacin, ornidazole, primaquine, promethazine, quinacrine, salbutamol and tolterodine, a higher resolution was achieved using anionic β-CDs. Nevertheless, for amlodipine, carvedilol, quinocide, sibutramine, sotalol and tafenoquine the resolution was better when neutral β-CDs were employed.

As it is known, the chiral separation of drugs with CDs could be improved by optimizing the CD concentration [17, 19-21, 23, 24, 31-41], the BGE pH [15, 20, 21, 24, 25, 27, 28, 33-35, 38, 39], the buffer co-ion [18-21, 23, 24, 28], by adding organic solvents (e.g., acetonitrile, methanol, ethanol, isopropanol) [17] [28] [24] [31] [38] [42-44] or other additives such as cations (e.g., guanidine) [45], surfactans (e.g., SDS) [43] and PEG 4000 [46]. Many articles have shown an increase in the enantiomeric resolution when increasing the CD concentration [17, 32, 35, 38, etc]. This can be justified by the higher number of interactions that may occur between analytes and the CD. Moreover, when increasing the CD concentration, the viscosity of the BGE increases and the EOF decreases, giving rise to longer migration times generating further opportunities for interactions between the analyte and the CD molecules. However, various studies also showed that when the CD concentration is continuously increased, a maximum value for the enantioresolution is reached depending the optimum CD concentration on the binding affinity of the analyte and the CD [19, 36, etc]. When the concentration of the CD is raised over an optimum value, the resolution can decrease due to the fact that all analyte molecules are complexed and the separation depends on the differences in the electrophoretic molibities of both enantiomer-CD complexes which are very similar. Furthermore, the decrease in the EOF due to the increase in the viscosity of the BGE originates longer migration times, leading to peak width broadening and decreasing further the resolution [24, 33, 39, 40].

An inversion in the migration order of the enantiomers may be observed when increasing the CD concentration. This was the case of the separation of sibutramine enantiomers with β-CD and acetyl-β-CD (A-β-CD) (Figure 1) [41] or of tolterodine and methoxytolterodine enantiomers with S-α-CD and S-β-CD [23]. This phenomenon can be justified taking into account that when the CD concentration is sufficiently high, most of the analyte molecules exist as CD complexes and the migration is determined by the electrophoretic mobility of the inclusion complexes and not by the affinity of enantiomers to the CD. As a consequence, a reversal in the migration order may be produced [1, 47-51].

When a non-satisfactory enantioseparation was obtained using a single CD system, dual chiral systems consisting of two different CDs [25, 52-56] or a CD plus a chiral ionic liquid (IL) [57-60], a chiral antibiotic [61], a polysaccharide [62] or a crown ether [63] were investigated in order to improve the chiral resolution (see Table 3). A mixture of two different CDs may increase the enantioseparation based on the differences in the complexation mechanisms of the two CDs with the enantiomers. In this regard, various dual CD systems were studied in the separation of the stereoisomers of six tetrahydronaphthalenic derivatives which are new potential agonist and

antagonist melatoninergic ligands. Good results were obtained with HS-β-CD + α-CD, HS-β-CD + γ-CD, HS-β-CD + HP-α-CD and HS-α-CD + HP-γ-CD [53]. In order to enhance the enantioresolution of meptazinol intermediate III and intermediate IV, dual CD systems of mono-6-deoxy-6-piperidine-β-cyclodextrin in combination with three different neutral CDs (β-CD, trimethyl-β-CD (TM-β-CD) and HP-β-CD) were tested [54]. The dual CD system consisting of mono-6-deoxy-6-piperdine-β-CD and HP-β-CD was shown to be the most efficient to enhance the simultaneous enantioresolution of both intermediates (Figure 2). Mixtures of CDs and ionic liquids (IL) have also shown a high potencial to enhance enantiomeric separations. It has been demonstrated, for example, the synergistic effect of the ionic liquid (1-ethyl-3-methylimidazolium-L-lactate) plus a CD (HP-β-CD or β-CD) in the enantioseparation of a large number of chiral drugs (Figure 3) [57, 58].

The migration times of analytes can frequently shift with uncoated capillaries due to the difficulty in controlling EOF. Internal standards may be used to correct such shifts. Another approach is to modify the internal capillary wall with an appropriate reagent. In this regard, a new type of chemically modified capillaries having diol groups was developed and applied to the chiral analysis of methamphetamine and related compounds by CE with CDs (β-CD and dimethyl-β-CD (DM-β-CD)). The migration time of each enantiomer in urine of methamphetamine addicts was the same as each enantiomer had in a standard solution. Thus, it was possible to identify enantiomers without any correction. On the other hand, with untreated fused-silica capillaries, the shifts of migration times of these enantiomers were too large to allow identification [56]. The repeatability and chiral resolution achieved with four types of chemically modified capillaries (FunCap-CE/Type D (possessing diol groups), Type A (amino groups), Type C (carboxyl groups), and Type S (sulfate groups)) which were used for the CE separation of methamphetamine enantiomers with S-γ-CD were evaluated. The best results were obtained with type S capillaries [64]. In a later study, Type S capillaries were employed to carry out the simultaneous chiral separation of 8 amphetamine-type stimulants (amphetamine, methamphetamine, norephedrine, norpseudoephedrine, ephedrine, pseudoephedrine, dimethylamphetamine and methylephedrine) with S-γ-CD by CE/MS/MS. A good repeatability of migration times and a high identification power of analytes were obtained due to the use of the MS/MS detection system [65].

Non-aqueous BGEs in CE (NACE) have not extensively been used in the enantioseparation of drugs with CDs in this period. The main advantages of NACE to achieve the enantiomeric analysis of drugs are the ability to dissolve hydrophobic analytes, lower conductivity, compatibility with mass spectrometric detection, feasibility of ion-pair formation, etc. Moreover, organic solvents possess lower dielectric constants than water, and intermolecular interactions between de CD and the analyte are promoted favouring the chiral discrimination. There are various articles in which aqueous and non-aqueous media are compared in the separation of chiral drugs [66-68]. Significant differences were found between the separation mechanisms in both media. For example, the enantiomers of propranolol formed inclusion complexes with HDMS-β-CD in aqueous BGEs and external type complexes in methanolic BGEs, and the opposite was true with HDAS-β-CD [66].

Microfluidic chip-CE devices were developed and applied to the chiral analysis of drugs. The simultaneous enantioseparation and determination of anisodamine (AN), atenolol (AT), and metoprolol (ME) in human urine was carried out using CM-β-CD as chiral selector (see Figure 4). The microfluidic-CE device developed incorporated on-chip dilution to facilitate the large number of dilutions which are required for the optimization process. Electrochemiluminescence

(ECL) detection was used to improve detection sensitivity. The methodology developed allowed to obtain important information for the treatment of stroke patients [69].

3. Enantioseparation mechanisms in CE with cyclodextrins

The separation mechanism of enantiomers in CE using CDs as chiral selectors is usually based on the formation of inclusion complexes where the enantiomer analyte fits into the CD cavity. The cavity size of the CD and the shape and structure of the analyte are important factors for chiral recognition. Furthermore, interactions between functional groups of the analyte and the hydroxyl groups on the CD-rim are also responsible for the chiral recognition and separation.

The characterization of interactions of enantiomers with CDs is a helpful tool in chiral CE research for a better understanding of the separation mechanism and the prediction of migration behaviour. Generally, the difference between the electrophoretic mobility for both enantiomer-CD complexes is negligible, and the separation is determined by their different stability constants. The stability constants and the electrophoretic mobilities of inclusion complexes of sibutramine enantiomers with methyl-β-CD (M-β-CD) were determined. The stability constant was higher for the (R)-enantiomer than for the (S)-enantiomer. However, the electrophoretic mobilities of both sibutramine enantiomer complexes were the same. Therefore, the separation of sibutramine enantiomers was mainly due to the different stability constants of the inclusion complexes [18].

Rarely, there is an inversion of the enantiomer migration order when the chiral selector concentration is increased. At low β-CD and A-β-CD concentrations, (S)-sibutramine migrated faster than (R)-sibutramine. However, at higher CD concentrations, (R)-sibutramine migrated faster than (S)-sibutramine. To explain this phenomenon, the binding constants and the electrophoretic mobilities of the inclusion complexes of sibutramine β-CD and sibutramine A-β-CD complexes were determined. At low β-CD and A-β-CD concentrations, the migration order was determined primarily by the stability of the complexes since most of the enantiomer molecules in solution are unbound. At higher β-CD and A-β-CD concentrations, most of the enantiomer molecules existed as CD complexes and the migration order was determined by the electrophoretic mobility of the complexes [41].

An alternative to the conventional direct technique to determine stability constants is the use of partial (PFT) and complete (CFT) filling techniques in which the capillary is partially or totally, respectively, filled with the chiral selector solution prior to the injection of the analyte, while the BGE remains without chiral reagent. Using CFT may ensure that enantiomers do not exit to the CD plug during the electrophoretic separation, simplifying the calculations. In this regard, a CFT technique was used to determine the stability constants of enantiomer-CD complexes of four antihistamines (dimethindene, promethazine, orphenadrine and terfenadine) and four antidepressants (bupropion, fluoxetine, nomifensine and viloxazine) drugs with HS-β-CD [70].

Nuclear magnetic resonance (NMR) has extensively been employed to know the structure of the inclusion complexes formed between the enantiomers of chiral drugs and CDs to explain the molecular mechanism underlying the behaviour observed in chiral CE. Structural differences were observed by using monodimensional rotating frame nuclear Overhauser effect spectroscopy (1D ROESY) between the complexes of propranolol with native β-CD and HS-β-CD in aqueous BGEs, which can explain the migration order of propranolol enantiomers using these two CDs as chiral selectors [71]. The structure of complexes formed between propranolol enantiomers and HDMS-β-CD and HDAS-β-CD in aqueous and non-aqueous media were determined by 1D ROESY to explain the electrophoretic behaviour. The enantiomers of

propranolol form inclusion type complexes with HDMS-β-CD in an aqueous BGE but external type complexes in a methanolic BGE, and the opposite was true for HDAS-β-CD [66]. Enantioselective ROESY experiments indicated that S-propranolol formed a tighter complex with HDAS-β-CD than R-propranolol [72]. 1D ROESY experiments showed a deeper inclusion of the aromatic moiety of the molecule of ephedrine enantiomers into the cavity of β-CD compared to α-CD, and this result suggests a stronger interaction between ephedrine and β-CD than between ephedrine and α-CD which is in good accordance with CE experiments [73]. The mechanism of chiral recognition between norephedrine (NEP) enantiomers with various CDs (α-CD, β-CD, HDMS-β-CD and HDAS-β-CD) in chiral CE was studied by 1H-NMR and 1D ROESY spectroscopy. Structures of analyte-CD complexes were proposed (Figure 5) [74]. The structure of the inclusion complexes of sibutramine enantiomers with M-β-CD was investigated by 1H-NMR and 2D ROESY spectroscopy. Not only the aromatic moiety but also methyl groups were included into the inner cavity of M-β-CD. The aromatic moiety would be positioned close to the narrow rim of M-β-CD and the methyl chain would be positioned near the large rim [75]. The effect of the cavity size of various CD derivatives (TM-α-CD, TM-β-CD and TM-γ-CD) on the separation of Ketoprofen enantiomers by chiral CE was studied by NMR. With TM-α-CD and TM-β-CD the (R)-enantiomer migrated first, whereas with TM-γ-CD the opposite happened. Based on NMR experiments different structures were proposed for each analyte-CD complex to explain the different affinity pattern of ketoprofen enantiomers toward these chiral selectors [76]. NMR experiments indicated that HP-β-CD formed a more stable complex with (R)-duloxetine than with (S)-duloxetine, and (S)-duloxetine bind to M-γ-CD more strongly than (R)-duloxetine. But enantiomer migration order obtained in CE experiments was not in agreement with these data. Therefore, enantioseparation may be determined by electrophoretic mobilities of inclusion complexes [77].

Molecular modelling techniques contribute to understand the enantioseparation mechanism and to predict the elution of enantiomers. Using molecular modelling techniques, optimized geometries for the lowest energy conformation for the inclusion complexes of ornidazole and ofloxacin enantiomers with S-β-CD were obtained. The stability of proposed geometries explained the different migration times observed in experimental studies [15]. Based on molecular simulation and theoretical calculations using computer-aided techniques, the order of elution of bupivacaine enantiomers in chiral CE with sulfobutyl ether β-CD (SBE-β-CD) was determined. The conformational energy of the complex formed by (S)-bupivacaine and SBE-β-CD was smaller than that of the complex between (R)-bupivacaine and SBE-β-CD [20]. Molecular modelling studies may significantly contribute to understand the nature of the intermolecular forces responsible for analyte–CD interactions and chiral recognition when they are used in combination with instrumental techniques, especially with ROESY experiments in NMR spectroscopy. A combination of molecular modelling and NMR was used to study the separation mechanism of enantiomers of the basic drugs bupivacaine and propranolol with the anionic CD derivatives HDMS-β-CD and HDAS-β-CD with NACE. For bupivacaine, 2D ROESY experiments showed that inclusion complexes were not formed, and the interaction of bupivacaine with CDs should involve the sulfate groups of the CD derivatives. In the case of propranolol, NMR experiments suggested that external complexes were formed between propranolol enantiomers and HDMS-β-CD while in the presence of HDAS-β-CD the alkyl chain of (R)-propranolol was assumed to enter into the CD cavity through the wider opening. The most energetically favourable geometries of the complexes between bupivacaine and propranolol enantiomers and both CD derivatives were determined by molecular modelling techniques and interaction energies were calculated in order to explain NACE experiments [78]. Molecular

docking and binding energy calculations between iodiconazole enantiomers and structurally related analogues with HP-γ-CD were carried out. Iodiconazole enantiomers were inserted into the hydrophobic cavity of HP-γ-CD. 2D NMR spectroscopy confirmed that conclusion. The mathematical equation proposed to calculate the enantiomeric resolution demonstrated good capability to predict the experimental chiral separation of these compounds in CE with HP-γ-CD [79]. A combination of isothermal titration calorimetry (ITC), NMR and molecular modelling techniques was used to provide a deeper understanding of the chiral recognition processes between β-CD or CM-β-CD and four chiral drugs (2-amino-1-phenyl-ethanol, 1-(4-methoxyphenyl)-2-(methylamine) ethanol, salbutamol sulfate and sotalol hydrochloride). When native β-CD was employed, no enantioseparation was obtained, but the enantioseparation was significantly improved with CM-β-CD. The ITC results showed that the high enantioseparation efficiency of CM-β-CD was associated with a strong binding affinity between drug molecules and chiral selector. However, the behaviour of salbutamol sulfate was an exception to this rule suggesting that the binding strength alone was not enough to explain the enantioseparation behaviour. The inclusion geometry obtained by autodock simulation was in agreement with the NMR experiments, and the calculated binding energies were also in agreement with the association constants obtained by ITC and with the CE enantioseparation results. Experimental results indicated that electrostatic interactions and hydrogen bonds play an important role in the enantiorecognition of these drugs with CM-β-CD [26]. Molecular modelling techniques have also been used in combination with MS for investigations of the enantiorecognition mechanism between drug enantiomers and CDs. A 1:1 stoichiometry for the inclusion complexes of ofloxacin enantiomers with HP-β-CD was obtained from MS studies. Quantum mechanics calculations of the binding energies for both enantiomers with the CD were in good accordance with the migration orders obtained in the CE experiments. And the most likely conformations for both enantiomer-CD complexes were generated by molecular mechanic calculations [60].

When a CD + IL dual chiral system was employed, as in the case of the CE enantioseparation of various chiral drugs by using HP-β-CD and the ionic liquid 1-ethyl-3-methylimidazolium-L-lactate ([EMIm][L-lactate]) in the BGE, the separation mechanism may be explained by the formation of an inclusion complex between enantiomers and CD, and the association of enantiomers with the IL either coated onto the inner capillary wall or free in the BGE. It has also been demonstrated that increasing the chain length of the cationic part of IL, the CE enantioseparation improved. Shorter alkyl chains (1-ethyl-3-methylimidazolium) are less hydrophobic than longer ones (1-butyl-3-methylimidazolium or 1-heptyl-3-methylimidazolium) and they formed a less stable bilayer inside the capillary, whereas a stable bilayer inside the capillary might allow a more stable environment for the separation of analytes. On the other hand, the nature of the anionic part of IL (L-lactate or Br) had little influence on the enantioseparation [57, 58].

4. Quantitative analysis

Chiral CE with UV detection was applied to quantitate drugs enantiomers. Table 4 summarizes the LODs obtained in the quantitative determinations. Some of the quantitative methods developed were applied to determine the enantiomers of the active ingredient in commercial formulations. The amount of sibutramine enantiomers was determined in two commercial formulations by using chiral CE with M-β-CD. There was no significant difference between values obtained and labelled amounts [18]. The enantiomers of ofloxacin and ornidazole using S-β-CD as chiral selector were determined simultaneously in tablets. A good agreement with the value claimed by the manufacturer was obtained. The LODs were 0.46 - 0.89 μg/mL [15]. For both

enantiomers of iodiconazole separated with chiral CE using HP-γ-CD, the LOD was 4.6 μg/mL [33]. A quantitative chiral CE method using CM-β-CD enabled the separation of meptazinol enantiomers with a LOD of 2.50 μg/mL. The method was applied to determine meptazinol in tablets [24]. Quantitation of sotalol enantiomers by chiral CE was carried out using the RAMEB. The LODs were 1.13 μg/mL for (R)-sotalol and 1.25 for (S)-sotalol. The method was suitable for the determination of sotalol in tablets [31]. The determination of amlodipine enantiomers using RAMEB as chiral selector in the BGE was achieved, being the LODs 2.31 μg/mL for the (R)-enantiomer and 2.43 μg/mL for the (S)-enantiomer. The method was applied to the enantiomeric determination of amlodipine tablets. The result was in good agreement with that declared by the manufacturers [27]. Moreover, the determination of carvedilol enantiomers was carried out using β-CD as chiral selector. The LODs were 1.13 μg/mL for the (R)-enantiomer and 1.18 μg/mL for the (S)-enantiomer. The method was applied to the analysis of tablets [28]. The enantiomeric quantitation of sibutramine was carried out by developing a method based on the use of M-β-CD. The LOD was 0.25 μg/mL and a 0.05% of (S)-enantiomer can be detected in a mixture of both enantiomers [75].

Several methods were applied to degradation studies of formulations. The use of SBE-β-CD enabled the quantitation of isradipine enantiomers in a pharmaceutical formulation. The LODs were 2.16 - 3.68 μg/mL. The method was also applied to the determination of isradipine enantiomers in degradation studies. The drug was subjected to oxidation, hydrolysis and photolysis. Isradipine enantiomers were separated from their degradation products and formulation excipients [32]. A CE enantioselective method with CM-β-CD was developed for the simultaneous quantitation of zopiclone enantiomers and its impurities in tablets. The method was applied to determine the degradation and racemization of zopiclone under stress conditions (acid and alkaline hydrolysis studies, oxidative studies and photo degradation studies). LODs for impurities were from 0.01 to 0.02 μg/mL [80].

Other quantitative methods were applied to the determination of the enantiomeric purity of pharmaceutical formulations. Thus, a stereoselective CE assay was developed for the determination of the enantiomeric purity of chloroquine using SBE-β-CD as chiral selector. The LOD was 0.6 μg/mL for both enantiomers. The method was applied to analyze the enantiomeric purity of synthetic samples. A 0.24% of (S)-enantiomer can be detected in a mixture of both enantiomers [81]. When using S-β-CD, the LOD for the (S)-cetirizine enantiomer was 0.075 μg/mL. The developed method allowed to determine at least 0.1% (w/w) of the (S)-cetirizine impurity. The method was applied to the enantiomeric purity control of (R)-cetirizine dihydrochloride tablets [35]. The (R)-enantiomer of ornidazole is an enantiomeric impurity in starting materials and pharmaceutical formulations of levornidazole. A chiral CE method with S-α-CD was developed to determine levornidazole and its enantiomeric impurity in levornidazole injection solutions. The LOD was 0.3 μg/mL (0.006%) [21]. Also, the determination of the optical impurity (S)-tolterodine by chiral CE with P-γ-CD was achieved. The LOD was 0.33 μg/mL. The proposed method was capable of determining 0.2% of (S)-tolterodine in pills [23]. In addition, the determination of the enantiomeric impurity of (R)-amlodipine at the 0.2 % level was carried out by CE using CM-β-CD. The LOD was 1.0 μg/mL. The method was applied to determine the enantiomeric purity of levamlodipine in bulk samples [39]. Chiral CE was also successfully applied to the enantiomeric purity determination of valsartan using A-β-CD into the BGE. The LOD for the (R)-enantiomer impurity was 0.01 %. The assay was applied to commercial products [34]. On the other hand, a dual system was employed enabling the quantitation of ofloxacin enantiomers using HP-β-CD and the ionic liquid 1-ethyl-3-methylimidazolium-L-lactate. The LOD for (R)-ofloxacin was 0.53 μg/mL. The method was applied to determine the chiral impurity (R)-

ofloxacin in bulk samples of (S)-ofloxacin. The amount of the chiral impurity was well below 0.2% [57]. Also, the chiral purity of eszopiclone in commercial tablets was determined by using a CD-IL dual system (β-CD and 1-ethyl-3-methylimidazolium-L-lactate). The concentration of the chiral impurity (R)-zopiclone was < 0.1% and the LOD value for the impurity (R)-zopiclone was found to be 0.3 μg/mL [58].

5. Sensitive analytical methodologies

Sensitive analytical methodologies are especially required when biological fluids are analyzed. Alternative detection systems to UV detection and preconcentration methods have been applied in chiral CE in order to obtain the necessary sensitivity [82, 83].

Regarding detection sensitivity, it is a critical point in CE when low LOD is required. The concentration sensitivity obtained in CE with UV detection is usually low due to the short optical path length (50–100 μm). To improve the LOD, detection systems of higher sensitivity than UV detection have been employed. Thus, bupropion enantiomers were resolved and quantitated in a pharmaceutical formulation and in a spiked urine sample by CE using S-α-CD as chiral selector. A sensitized time-resolved phosphorescence detection mode was used. The LOD obtained for each enantiomer was $2x10^{-7}$ M (0.048 μg/mL), which means an improvement of the sensitivity by a factor of more than 10 over that achieved with UV detection. A home-built detection system was used. The excitation energy from a pulsed laser at 266 nm is transferred from the analyte to an acceptor (1-bromo-4-naphthalenesulfonic acid) followed by time-resolved phosphorescence detection. Time resolution avoids light scattering problems and fluorescence due to impurities into the sample, since the lifetime of phosphorescence is larger than fluorescence. The sensitized phosphorescence mode is particularly well suited for analytes with poor phosphorescence. In this mode, the analyte acts as an energy donor to a phosphorescent acceptor [84].

Conductivity detection enables to analyze non-UV-absorbing compounds with good sensitivity without chemical derivatization. A quantitative method was developed for the analysis of bupivacaine using conductivity detection. The method was applied in rabbit serum and pharmaceutical injections. The LODs were 0.26 μg/mL and 0.052 μg/mL, respectively probably due to worse S/N ratio in the serum samples. Compared with UV detection, conductivity detection has a clear advantage in trace analysis [20].

Anisodamine, atenolol, and metoprolol enantiomers were separated and quantitated in spiked human urine by using a microfluidic chip-CE device and CM-β-CD as chiral selector and electrochemiluminescence detection. LODs were in the range 0.3-0.6 μM (0.08-0.18 μg/mL) [69].

A CE-ESI-MS/MS assay using succinyl-γ-CD (Succ-γ-CD) was developed and applied to the determination of L- and D-carnitine in pharmaceutical formulations (ampoules, oral solutions, sachets, and tablets). The LOD for both enantiomers was of 0.010 μg/mL allowing to detect a 0.002% of the D-enantiomer impurity with respect to the main L-enantiomer [85]. UV and TOF-MS detection were compared in the separation of 12 cathinone analogues. The MS detector provided lower LODs for nine out of 12 analytes [38]. The enantiomeric purity of duloxetine was determined by chiral CE with HP-β-CD and UV detection at 220 nm, and with MS detection. The LODs were 0.2 μg/mL by CE-UV and 0.02 μg/mL by CE-MS, enabling to detect 0.02% of enantiomeric impurity [86]. To avoid the suppression effect of the MS signal by CDs, the partial filling technique of the capillary is commonly used, but resolution may be negatively affected. In this regard, low-flow nano-ESI was applied to the CE enantioseparation and detection of cathinones with HS-γ-CD, no significant MS signal suppression was observed, and enhanced

enantioresolution was obtained due to the presence of the HS-γ-CD into the entire capillary during the analysis [63].

With respect to preconcentration methods, electromembrane extraction (EME) and dispersive liquid–liquid microextraction (DLLME) were employed to improve LODs in the analysis of chiral drugs by CE.

In EME methods, ionized analytes are extracted from sample solutions through a supported liquid membrane (SLM) on a porous hollow fiber, into an acceptor solution located inside the lumen of the hollow fiber by applying an electrical field across the wall (Figure 6). An EME preconcentration method was developed for the determination of trimipramine in plasma and urine samples. The extract was analyzed by using CE with α-CD. The LOD for both enantiomers was 7 ng/mL [36]. Amlodipine enantiomers were extracted from plasma and urine samples using and EME method with a supported liquid membrane consisting of 2-nitrophenyl octyl ether impregnated on the wall of a hollow fiber. The enrichment factor obtained was about 124. The extract was analyzed by chiral CE using HP-α-CD, and the LOD for both enantiomers was 3-5 ng/mL [87]. Enrichment factors in the range of 108-134 for propranolol enantiomers from urine and plasma samples were obtained using an EME method and CE with HP-β-CD (Figure 7). The LODs obtained for both enantiomers in urine and plasma samples were 7 and 10 ng/mL, respectively. 2-Nitro phenyl octylether was used as the supported liquid membrane. [37].

When a DLLME method is used, an extraction and a disperser solvent are mixed with the aqueous sample to form a cloudy solution. After the extraction of analytes is achieved, phases are separated by centrifugation. The extract is evaporated to dryness and the residue is reconstituted in a small volume for injection into the CE system. The chiral separation and determination of several illicit drugs (DL-methamphetamine, DL-3,4-methylenedioxymethamphetamine and DL-ketamine) in prepared forensic samples (banknotes, kraft paper, plastic bag and silver paper) was made by using a DLLME method for sample preparation and a chiral CE system with β-CD and UV detection at 200 nm. The LODs were between 0.08 and 0.2 ng/mL [88]. The determination of hydroxyzine and cetirizine enantiomers in liquid culture media was achieved by using CE with S-β-CD as chiral selector and UV detection at 214 nm. The hydroxyzine and cetirizine enantiomers were extracted using a DLLME method. The LODs were 0.037 and 0.075 μg/mL, respectively, for cetirizine and hydroxyzine [22]. A DLLME preconcentration method was developed for the enantioselective analysis of zopiclone and its metabolite N-desmethylzopiclone by chiral CE using CM-β-CD and UV detection at 310 nm after fungal biotransformation (Figure 8). The LODs for zopiclone and N-desmethylzopiclone were 0.27 and 0.15 ng/mL, respectively. The fungal biotransformation of zopiclone to N-desmethylzopiclone was demonstrated to be enantioselective [25]. A DLLME method in combination with CE-field amplified sample injection (FASI) was developed for the chiral separation and determination of carvedilol in human plasma using CM-β-CD and UV detection at 241 nm. LODs for both enantiomers were 4 ng/mL [40].

A FASI method was developed to improve the detection sensitivity of pindolol, oxprenolol and propranolol enantiomers separated by CE with a dual CD system (DM-β-CD + TM-β-CD) and achiral ionic liquids as modifiers. The LODs were between 0.11 and 0.26 ng/mL. The method was applied to the analysis of spiked urine samples [55].

6. Metabolism of drugs

Chiral CE has shown a high potential to carry out metabolic studies of chiral drugs to investigate the stereoselectivity of metabolic steps.

Ketamine is metabolized by the hepatic cytochrome P450 (CYP) enzyme system through N-demethylation to norketamine followed by hydroxylation of norketamine. The stereoisomers of ketamine and its metabolites were analyzed by CE using S-β-CD to identify cytochrome P450 enzymes involved in hepatic ketamine and norketamine biotransformation *in vitro*. Ketamine and norketamine enantiomers were incubated with different types of CYP enzymes. The data suggested that *in vitro* biotransformation of ketamine and norketamine is stereoselective [89]. Moreover, the CYP3A4-catalyzed N-demethylation kinetics of ketamine to norketamine and its inhibition by ketoconazole *in vitro* was investigated by CE using HS-β-CD and γ-CD as chiral selectors. Data obtained showed that CYP3A4-catalyzed N-demethylation is stereoselective, and the inhibition by ketoconazole is not stereoselective. CYP3A4 is an enzyme responsible for the metabolism of more than 50% of commonly prescribed drugs [90]. HS-γ-CD was used to study the stereoselectivity of the metabolism of ketamine to norketamine via CYP3A4. The separation capillary was used itself as a microreactor for the enzymatic transformation of ketamine to norketamine via CYP3A4, followed by the on-line chiral CE separation and determination of reaction products. Figure 9 shows the increase in the production of the (S)-norketamine enantiomer over the (R)-enantiomer [91]. The proposed method was subsequently improved with a simplification of the composition of the reaction mixture, the omission of the capillary cooling step used previously, prolongation of the total capillary length, increase of the HS-γ-CD concentration and other parameters such as the number and secuence of plugs of enzyme and reactant solutions and the pressure used to introduce the plugs. The LOD was 0.8 μM (0.18 μg/mL) for both norketamine enantiomers [92]. An enantioselective CE assay using S-β-CD as chiral selector for the separation of ketamine and its metabolites was applied to the *in vitro* study of the enantioselectivity of the metabolism of ketamine in microsomes of different species (humans, horses and dogs). It was demonstrated that ketamine was metabolized enantioselectively in all three species. A LOD of 0.02 μg/mL for ketamine and norketamine was obtained [93]. The enantioselective distribution of ketamine and norketamine in equine brain and cerebrospinal fluid (CSF) was investigated by chiral CE with S-β-CD. After injection of racemic ketamine, all enantiomers of ketamine and norketamine were detected in CSF and brain. After injection of S-ketamine, only S-ketamine and S-norketamine were detected. The LOD was 8 ng/mL for both ketamine and norketamine enantiomers. A Liquid-liquid pre-concentration method was used [94].

7. Criminalistic and forensic investigations

As above mentioned, a chiral CE method with β-CD using a DLLME procedure for sample preconcentration was applied to the enantioseparation and determination of illicit drugs (heroin, DL-methamphetamine, DL-3, 4-methylenedioxymethamphetamine and DL-ketamine) in prepared forensic samples (banknotes, kraft paper, plastic bag and silver paper) [88].

Chemically modified capillaries were applied to the enantiomeric analysis of methamphetamine and related compounds in urine samples of methamphetamine addicts using CE with β-CD and DM-β-CD [56] and to the analysis of amphetamine-type stimulants (amphetamine, methamphetamine, norephedrine, norpseudoephedrine, ephedrine, pseudoephedrine, dimethylamphetamine and methylephedrine) in forensic samples by CE/MS/MS using S-γ-CD [64, 65]. Moreover, methamphetamine profiling (methamphetamine, amphetamine, ephedrine, pseudoephedrine, norephedrine, and norpseudoephedrine) of different seizures was carried out by CE with HS-γ-CD [64] and the enantioseparation of 13 new amphetamine-like designer drugs was possible by CE using S-β-CD [42]. Also, the chiral CE separation of 12 cathinone analogues was achieved using HS-γ-CD and TOF-MS detection and the method was validated

and applied to examine seized drugs. Mass spectrometry is a valuable technique for the identification of individual analytes present in seized drugs [38].

Conclusions

Proper selection of the type of CD to be used to achieve enantiomeric separations of chiral drugs by CE is paramount. The best separations were obtained with CDs that possess negatively charged substituents, because the electrophoretic mobility of these CDs has opposite direction to that of the EOF and the migration time of the analyte is increased. As a consequence, the interactions between the analyte and the CD also increase. Moreover, the fact that many drugs have basic character and are positively charged in solution at acidic pH and they have higher affinity for negatively charged CDs, increases the recognition capability between them. β-CDs are the most commonly used chiral selectors for these compounds. In some cases, synergistic effects were observed when CDs are used together with other chiral selectors in dual chiral systems.

NMR studies and computational simulation techniques have been applied to establish the structure of analyte-CD complexes and the mechanism of recognition and enantioseparation by chiral CE. The value of the stability constant of the analyte-CD complex plays an important role to interpret the electrophoretic behavior and the order of elution of both enantiomers.

Many applications of CE to the enantiomeric analysis of chiral drugs have been reported, such as the quantitative analysis of pharmaceutical formulations and their enantiomeric purity, the degradation studies of drugs, the analysis of drug enantiomers in biological samples and the study of their metabolism, as well as its application in criminalistics and forensic investigations of illegal drugs. Finally, the development of extraction and preconcentration methods (e.g., EME and DLLME) and the use of detection systems of high sensitivity (e.g, time-resolved phosphorescence, electrochemiluminescence, conductivity and MS) enabled to improve the LODs which increased the potential of the chiral CE methodologies.

Conflicts of interest

Authors declare that they have no conflict of interest

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FIGURE CAPTIONS

Figure 1. An electropherogram demonstrates the reversal of sibutramine enantiomer migration order using (a) native β-CD and (b) A-β-CD as chiral selectors. CE conditions: fused-silica capillary (uncoated, 50 µm i.d. x 54 cm, effective length 45 cm); injection, 50 mbar, 5 s; applied voltage, 251<V; temperature, 25 °C; buffer, 20 mM phosphate/10 mM citrate containing chiral selector, pH 4.3; detection, 223 nm. The highest concentration of β-CD and A-β-CD used in this experiment was 20 and 100 mM, respectively. (From ref. [41])

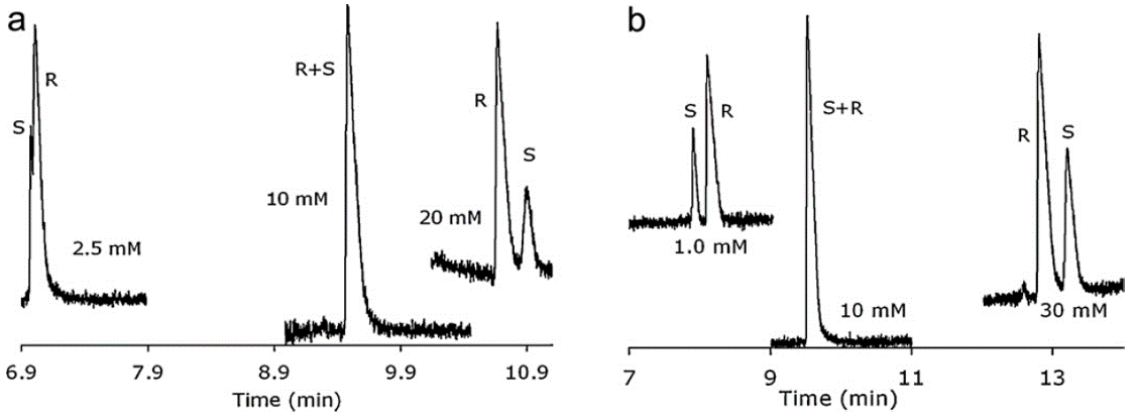

Figure 2. The electropherograms of enantiomeric separation of meptazinol and its three intermediates using single CD system. (A) Intermediate II; background electrolyte (BGE), 12.5 mmol/L mono-6-deoxy-6-piperdine-β-CD (PIP-β-CD), pH 3.0, 20 mmol/L phosphate buffer, 20 kV. (B) Meptazinol, intermediate III and intermediate IV; BGE, 7.5 mmol/L PIP-β-CD, pH 3.0, 20 mmol/L phosphate buffer, 20 kV. The electropherograms of enantiomeric separation of meptazinol, intermediate III and intermediate IV using HP-β-CD (HP- β-CD) and PIP-β-CD dual CD system. (C) BGE: 4.0 mmol/L HP-β-CD and 5.0 mmol/L PIP-β-CD, pH 3.0, 20 mmol/L phosphate buffer, 20 kV. (D) BGE: 40.0 mmol/L HP-β-CD and 5.0 mmol/L PIP-β-CD, pH 3.0, 20 mmol/L phosphate buffer, 20 kV. (From ref. [54])

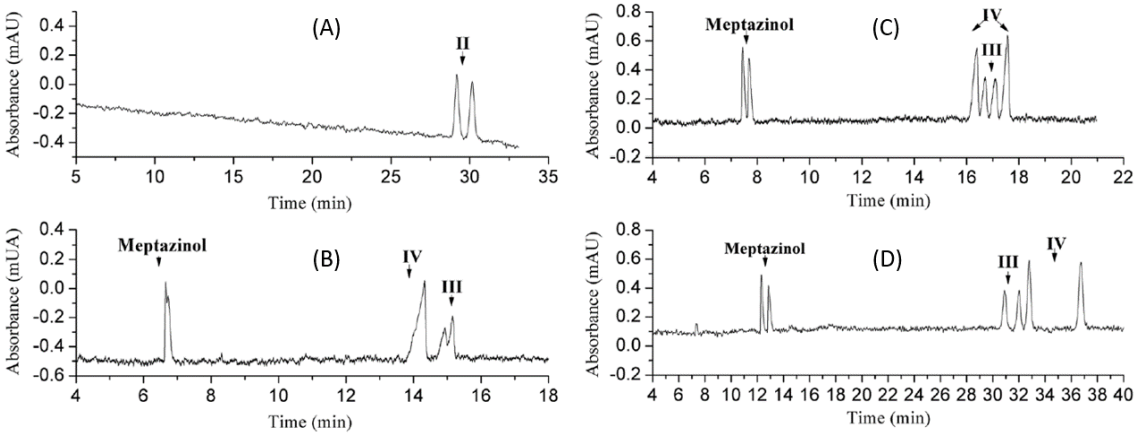

Figure 3. Electropherograms of the 10 analytes in the absence (A) and presence (B) of 1-ethyl-3-methylimidazolium-L-lactate in BGE (BGE: 40 mM HP-β-CD, 50 mM NaH_2PO_4-H_3PO_4, pH 2.75 with 30 mM 1-ethyl-3-methylimidazolium-L-lactate added); ofloxacin (1), propranolol (2), dioxopromethazine (3), isoprenaline (4), chlorpheniramine (5), liarozole (6), tropicamide (7), amlodipine (8), brompheniramine (9), and homatropine (10). (From ref. [57])

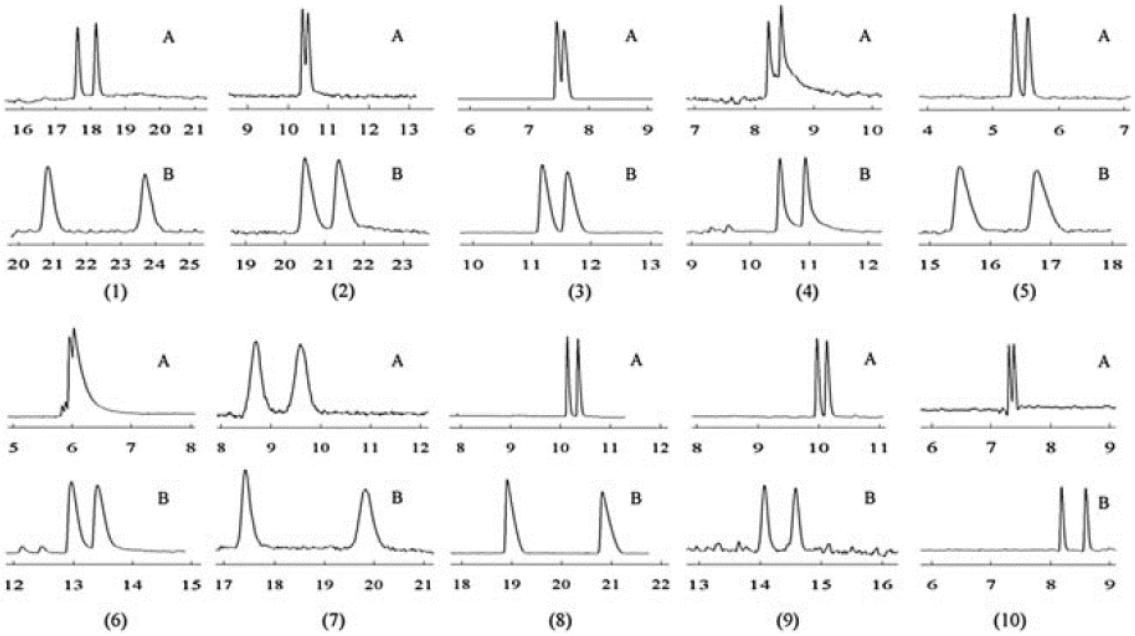

Figure 4. Typical electropherograms of (A) 60 μM anisodamine (AN), 50 μM atenolol (AT) and 30 μM metoprolol (ME) standard solutions; (B) 30-fold diluted blank urine sample, (C) 30-fold diluted urine spiked with AN, AT, and ME to the same conditions as (A); microchip-CE-ECL conditions: separation channel, around 55 cm effective length; sample injection, 10 kV × 10 s; separation voltage, 17.5 kV; running buffer, 57.6 mM HAc-NaAc (pH 5.3) − 14.7 mM CM-β-CD. (From ref. [69])

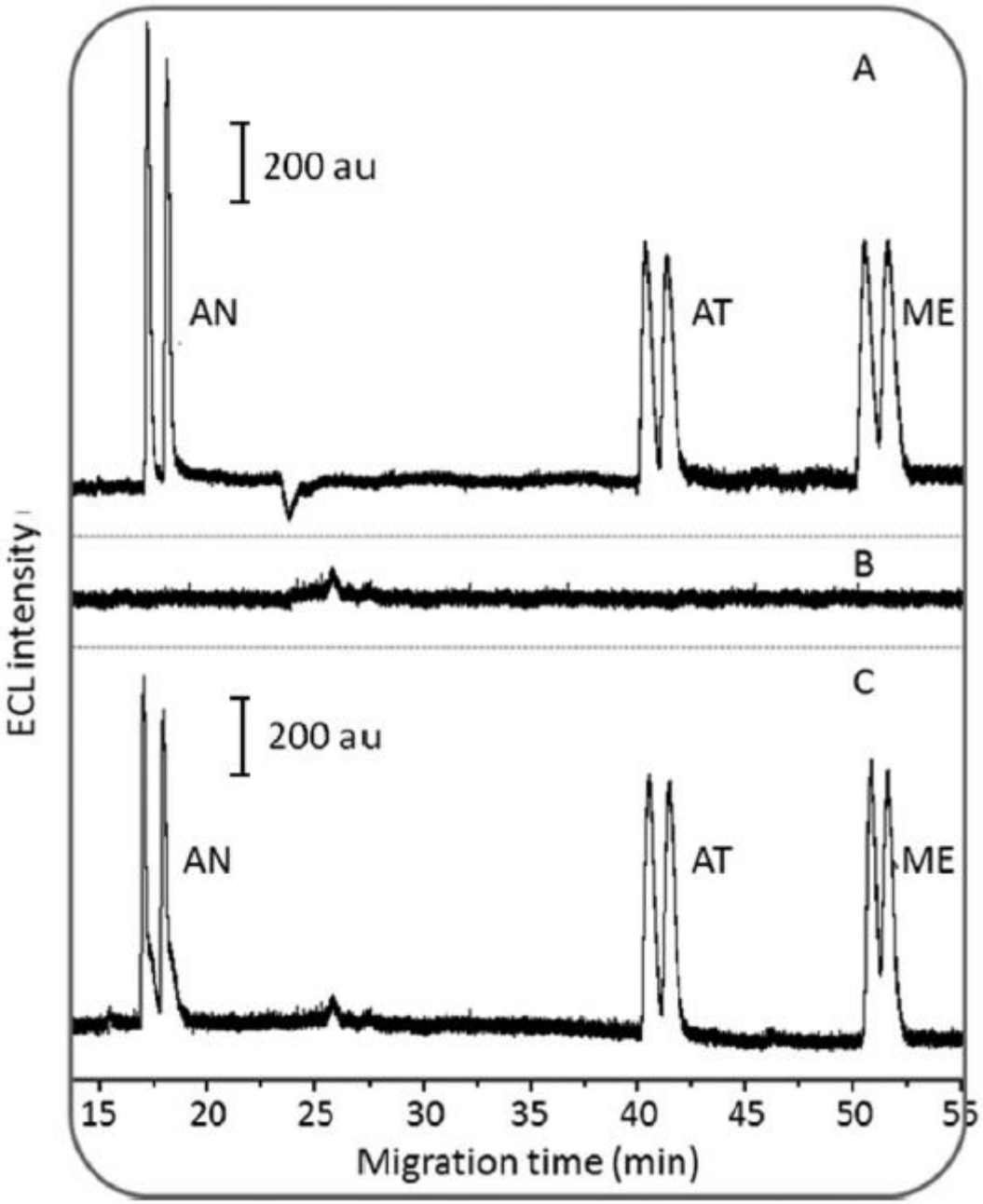

Figure 5. Structure of the norephedrine complexes with α-CD (A), β-CD (B), HDMS-β-CD (C), and HDAS-β-CD (D). (From ref. [74])

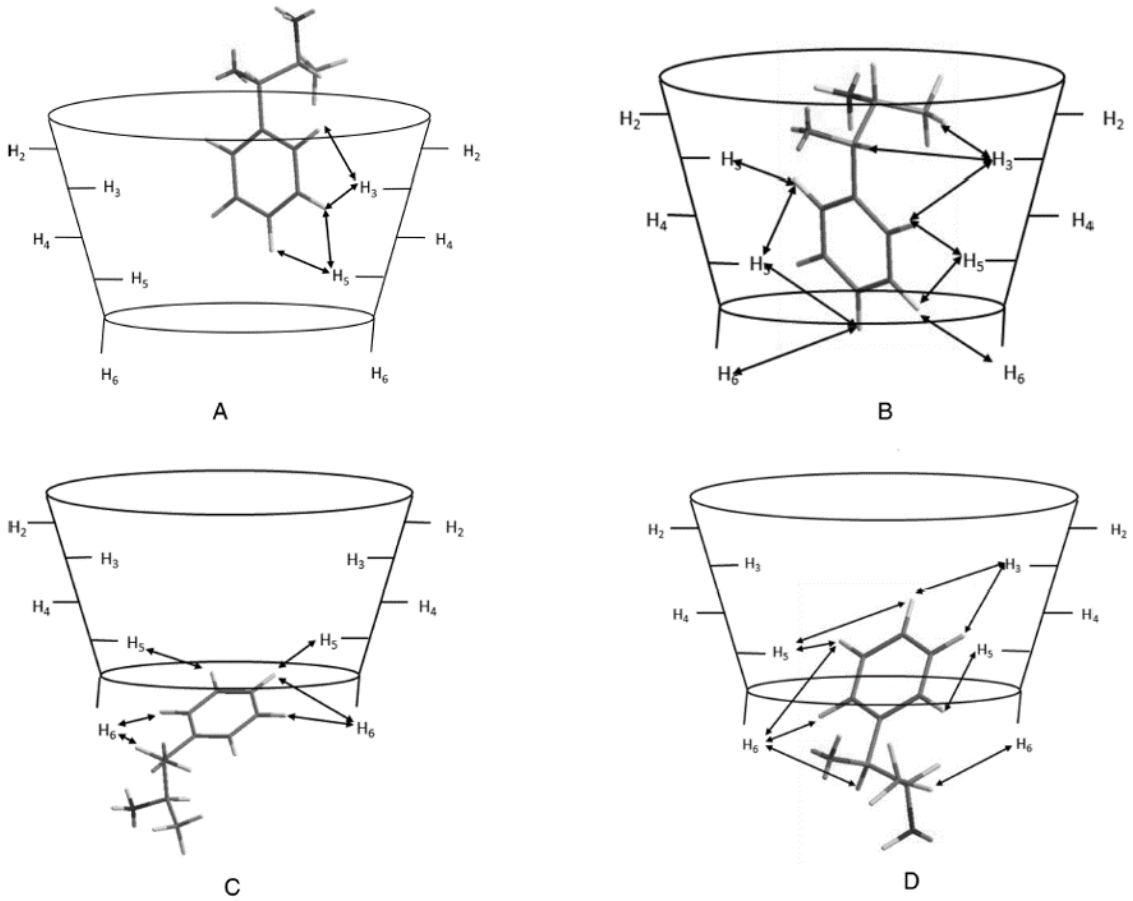

Figure 6. Schematic illustration of the setup for EME. (From ref. [87])

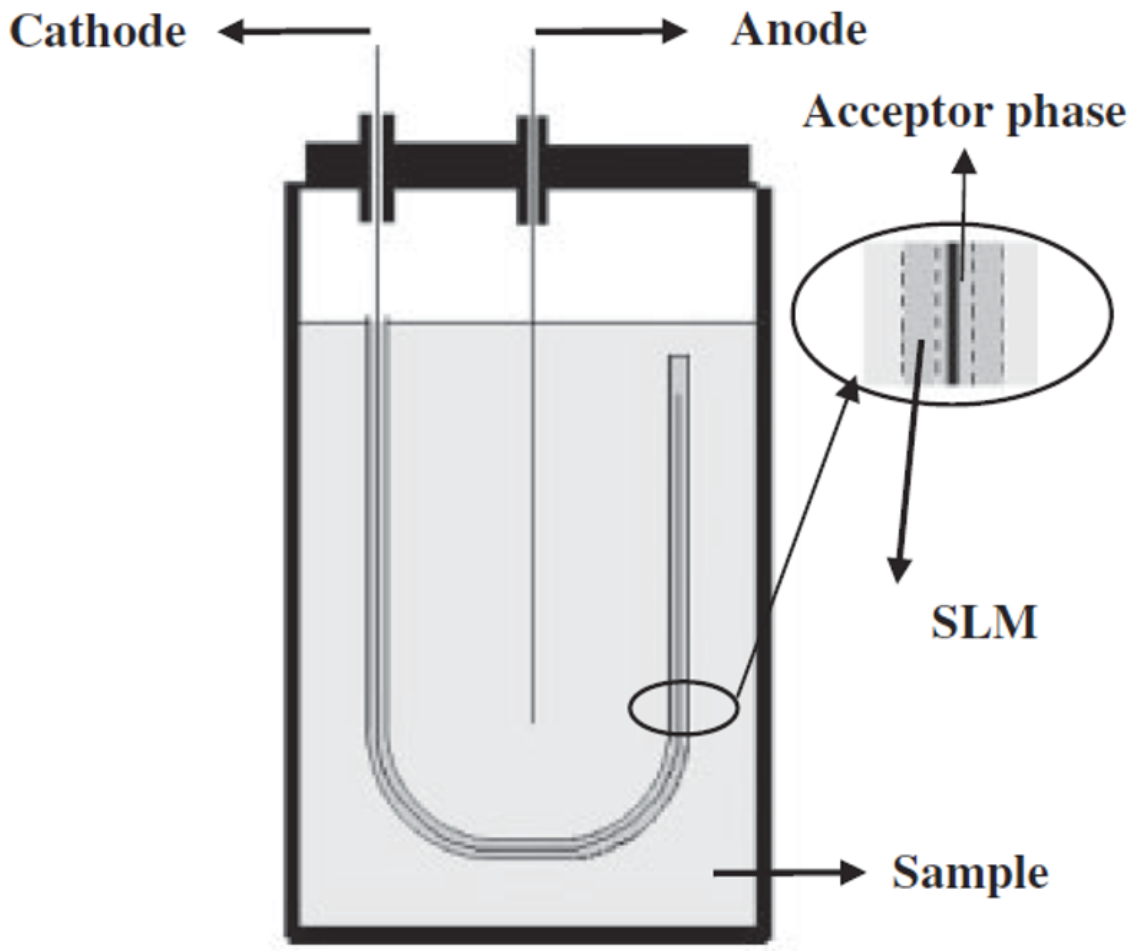

Figure 7. Electropherograms obtained after EME, (A) nonspiked urine sample, and (B) urine ample spiked with 100 ng/mL of each enantiomer. CE conditions: capillary: 60 cm (50 cm effective length) x 50 µm i.d; detection: 214 nm; applied voltage: 18 kV; temperature: 20° C; injection: 60 mbar x 5 s; separation solution: 80 mM ammonium acetate pH 2.5 containing 8mM HP-β-CD as chiral selector. (From ref. [37])

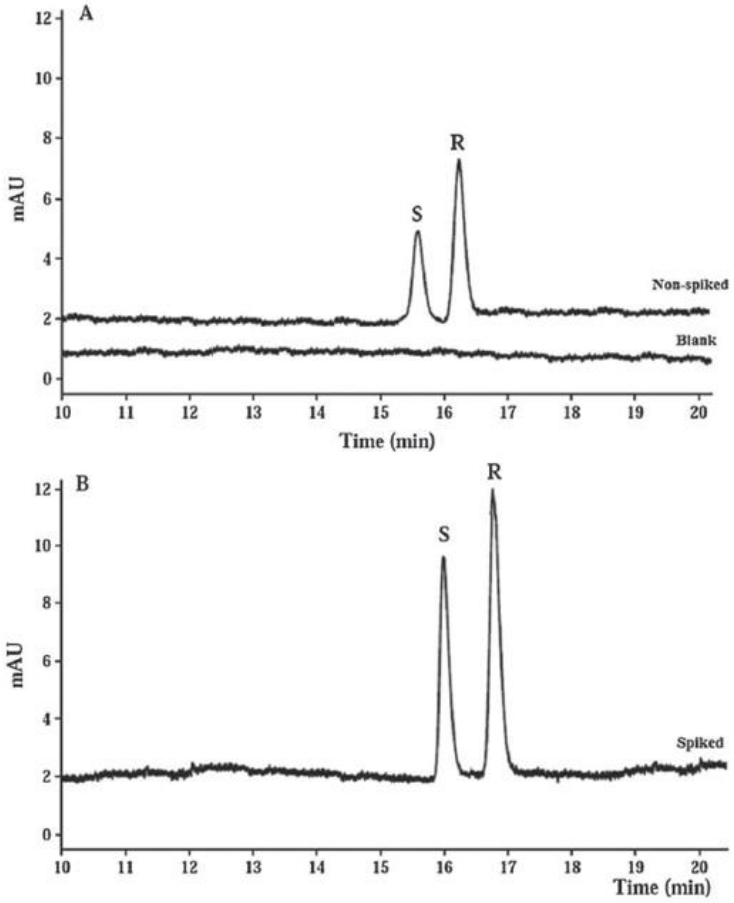

Figure 8. Representative electropherograms for the biotransformation of zopiclone (ZO) by the *Cunninghcimella* fungi after DLLME extraction. (A) Czapek liquid culture medium in the absence of ZO (sample control); (B) analysis of the Czapek liquid culture medium after the biotransformation period. (IS) Internal standard (rac-mirtazapine), ZO (zopiclone), N-Des-ZO (N-desmethylzopiclone). (From ref. [25])

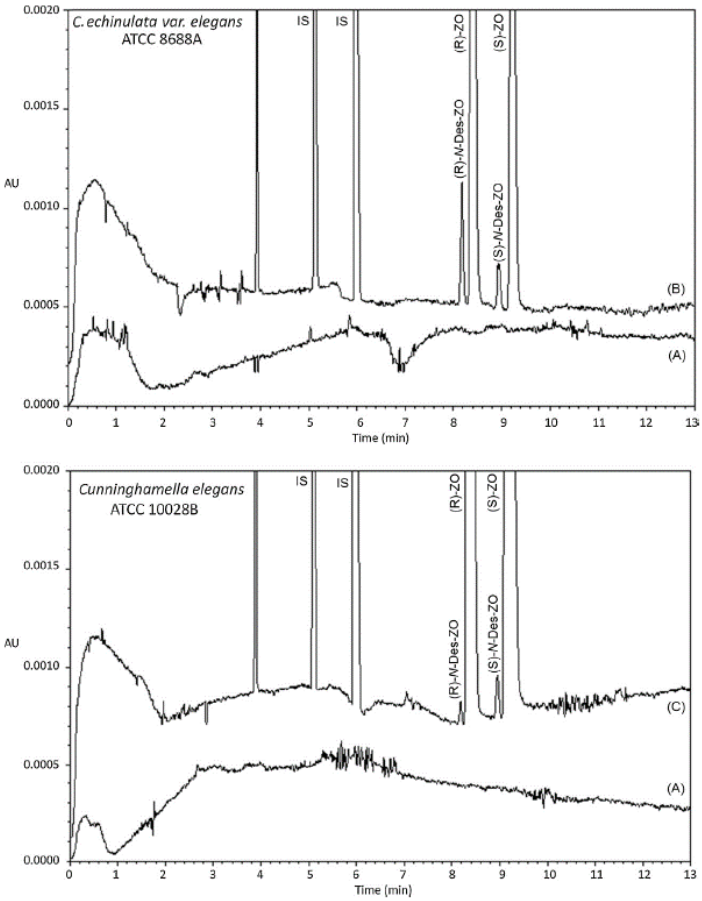

Figure 9. Norketamine enantiomer formation rate as function of ketamine enantiomer concentration by CYP3A4 after 8 min incubation with racemic ketamine at 37°C. Symbols denote the mean of duplicates. Solid and dotted lines are predicted values based on nonlinear regression analysis using the Michaelis-Menten equation and assuming a twofold dilution of the enzyme. Key: (●) S-norketamine (S-NK) and (○) R-norketamine (R-NK). (From ref. [94])

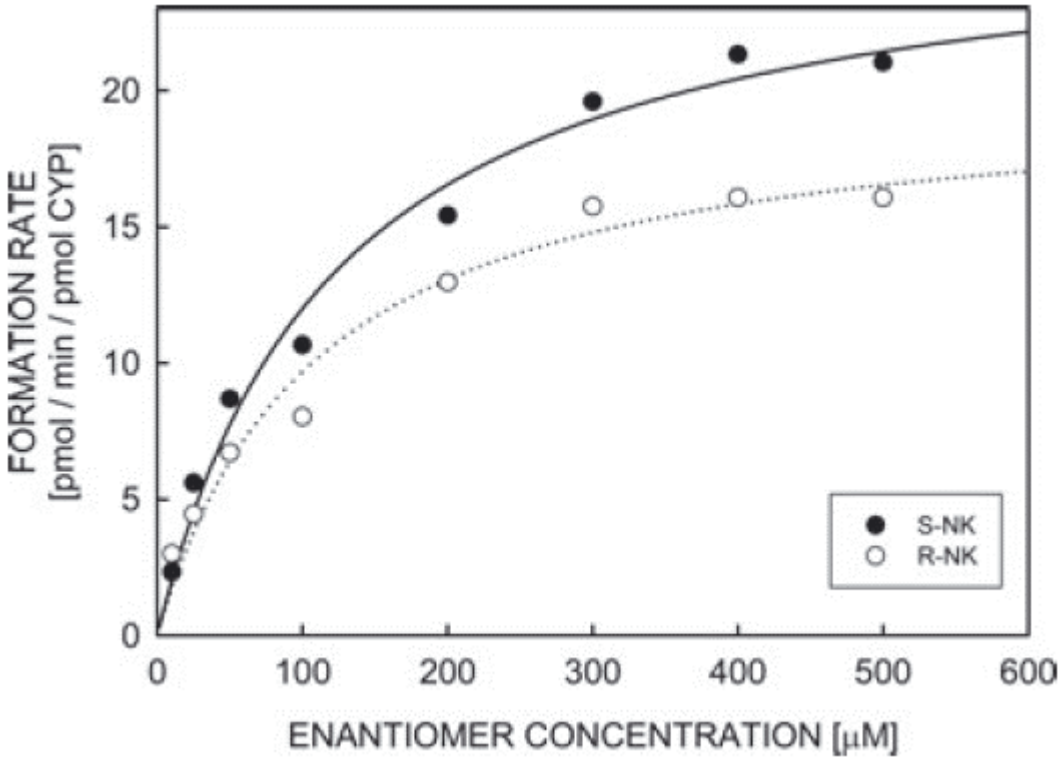

Table 1.- CDs employed in chiral CE for the enantiomeric separation of drugs and resolution values obtained (**NR:** unresolved, **R:** partially or totally resolved).

CD	Drug (Resolution)	Ref.
α-CD	amlodipine (1.4), chloroquine (NR), ephedrine (R), ibuprofen (NR), iodiconazole (NR), mefloquine (NR), methoxytolterodine (NR), naproxen (NR), norephedrine (R), ornidazole (NR), primaquine(NR), propranolol (0.1), propranolol (NR), quinacrine (NR), quinocide (NR), sotalol (NR), tafenoquine (NR), talinolol (NR), tamsulosin (2.4), tolterodine (NR), trimipramine (3.0), valsartan (NR)	16,21,23,27,31 34,36,37,46,67 71,73,74,79
β-CD	1-(4-methoxyphenyl)-2-(methylamine)ethanol (NR), 2-amino-1-phenyl-ethanol (NR), 1-(3,4-dimethylphenyl)-2-(methylamino)propan-1-one (R), 4-fluoromethcathinone (NR), amlodipine (0.86), amlodipine (NR), amphetamine (R), bambuterol (NR), brompheniramine (1.30), buphedrone (R), bupivacaine (NR), butylone (NR), carvedilol (2.74), carvedilol (1.12), cetirizine (NR), chloroquine (NR), chlorphenamine (1.16), citalopram (NR), clenbuterol (1.85), dimethylcathinone (R), dioxopromethazine (1.28), duloxetine (NR), duloxetine (NR), ephedrine (R), ethcathinone (R), ethylone (R), fenoterol (R), homatropine (1.21), homatropine (1.97), ibuprofen (0.8), iodiconazole (NR), iodiconazole (NR), ketamine (R), liarozole (1.45), 1-(Benzo[d][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one (R), mefloquine (0.30), mephedrone (R), mephedrone (NR), methamphetamine (R), methedrone (NR), methoxytolterodine (NR), methylenedioxymethamphetamine (R), methylone (R), naphyrone (NR), naproxen (0.5), nefopam (NR), norephedrine (R), ofloxacin (NR), ornidazole (NR), pentedrone (R), pentylone (R), primaquine (NR), procaterol (2.52), promethazine (1.15), propranolol (0.6), propranolol (R), quinacrine (NR), quinocide (NR), repaglinide (1.18), repaglinide (NR), salbutamol (NR), salbutamol (NR), sibutramine (0.92), sibutramine (1.1), sotalol (NR), sotalol (NR), tafenoquine (NR), talinolol (NR), tamsulosin (1.4), tolterodine (NR), trimipramine (0.5), tulobuterol (0.87), valsartan (NR), venlafaxine (0.76), zopiclone (0.78)	16,17,19,20,21 23,26,27,28,29 30,31,33,34,36 37,38,41,44,46 52,58,62,67,71 73,74,79,86,88
γ-CD	bambuterol (NR), butylone (NR), chloroquine (NR), clenbuterol (NR), duloxetine (NR), ephedrine (NR), fenoterol (NR), ibuprofen (NR), iodiconazole (NR), iodiconazole (NR), mefloquine (NR), mephedrone (NR), methoxytolterodine (NR), naphyrone (NR), naproxen (NR), norephedrine (NR), ornidazole (NR), primaquine (1.02), procaterol (0.46), propranolol (NR), quinacrine (NR), quinocide (NR), salbutamol (NR), sotalol (NR), tafenoquine (NR), tamsulosin (NR), tolterodine (NR), trimipramine (0.05), tulobuterol (0.56), valsartan (NR)	16,17,19,21,23 29,31,33,34,36 46,71,73,74,79 86
A-β-CD	duloxetine (NR), sibutramine (2.86), valsartan (3.08)	34,41,86
A-γ-CD	duloxetine (R), duloxetine (0.6)	77,86
CE-α-CD	chloroquine (NR), mefloquine (0.72), primaquine (NR), quinacrine (NR), quinocide (NR), tafenoquine (NR)	16
CE-β-CD	ornidazole (NR), chloroquine (NR), mefloquine (1.53), primaquine (NR), quinacrine (NR), quinocide (0.95), tafenoquine (NR)	16,21
CE-γ-CD	chloroquine (NR), mefloquine (0.73), primaquine (3.32), quinacrine (NR), quinocide (NR), tafenoquine (NR)	16
CM-α-CD	chloroquine (1.86), mefloquine (3.64), primaquine (19.64), quinacrine (NR), quinocide (0.45), tafenoquine (1.26)	16
CM-β-CD	1-(4-methoxyphenyl)-2-(methylamine)ethanol (R), 2-amino-1-phenyl-ethanol (R), amlodipine (1.55), amlodipine (9.8), anisodamine (R), atenolol (R), bambuterol (8.52), butylone (0.3), carvedilol (4.0), chloroquine (1.09), clenbuterol (7.65), desmethylzopiclone (> 2), isradipine (R), mefloquine (6.24), mephedrone (NR), meptazinol (2.03), methoxytolterodine (NR), metoprolol (R), naphyrone (1.9), primaquine (2.05), procaterol (25.37), quinacrine (1.67), quinocide (2.51), salbutamol (2.19), salbutamol (R), sibutramine (1.6), sotalol (NR), sotalol (R), tafenoquine (1.44), tolterodine (NR), tulobuterol (2.30), zopiclone (R), zopiclone (> 2), zopicloneoxide (> 2)	16,17,18,19,23 24,25,26,27,31 32,39,40,69,80

CM-γ-CD	chloroquine (NR), mefloquine (2.85), primaquine (9.18), quinacrine (NR), quinocide (1.00), tafenoquine (0.51)	16
DM-β-CD	duloxetine (NR), iodiconazole (NR), bambuterol (1.45), clenbuterol (3.07), ephedrine (R), fenoterol (NR), iodiconazole (NR), methoxytolterodine (NR), norephedrine (R), procaterol (4.82), propranolol (NR), repaglinide (1.8), salbutamol (0.97), talinolol (NR), tolterodine (NR), tulobuterol (1.00)	19,23,29,30,33 67,71,73,74,79 86
Glu-β-CD	naproxen (1.04), pranoprofen (NR), warfarin (0.62)	60
HB-β-CD	duloxetine (R), duloxetine (0.7)	77,86
HB-γ-CD	duloxetine (NR)	86
HDA-β-CD	ephedrine (R), norephedrine (R)	73,74
HDAS-β-CD	propranolol (R), acebutolol (< 1), atenolol (< 1), bupivacaine (R), carazolol (3.6), carteolol (2.9), carvedilol (1.3), ephedrine (R), norephedrine (R), propranolol (R), propranolol (R), propranolol (R), propranolol (3.9), sotalol (6.5), talinolol (R)	66,67,68,71,72 73,74,78
HDMS-β-CD	propranolol (R), acebutolol (1.2), atenolol (< 1), bupivacaine (R), carazolol (< 1), carteolol (< 1), carvedilol (< 1), ephedrine (R), norephedrine (R), propranolol (R), propranolol (R), propranolol (R), propranolol (3.3), sotalol (1.5), talinolol (R)	66,67,68,71,72 73,74,78
HE-β-CD	iodiconazole (NR), methoxytolterodine (NR), tolterodine (NR)	23,33
HP-α-CD	propranolol (0.3), chloroquine (NR), iodiconazole (NR), mefloquine (2.84), primaquine (1.46), quinacrine (NR), quinocide (NR), tafenoquine (NR), trimipramine (1.1), valsartan (NR)	16,34,36,37,79
HP-β-CD	amlodipine (2.17), amlodipine (R), amlodipine (2.33), bambuterol (0.57), bupivacaine (NR), butylone (NR), carvedilol (2.54), cetirizine (NR), chloroquine (NR), citalopram (NR), clenbuterol (0.45), duloxetine (> 1), duloxetine (NR), duloxetine (1.6), fenoterol (R), iodiconazole (NR), iodiconazole (NR), mefloquine (2.34), mephedrone (NR), methoxytolterodine (NR), naphyrone (NR), naproxen (1.95), nefopam (0.5), ofloxacin (R), pranoprofen (< 0.40), primaquine (NR), procaterol (5.56), propranolol (1.2), quinacrine (NR), quinocide (0.95), salbutamol (0.74), sibutramine (0.9), sotalol (0.73), tafenoquine (NR), tolterodine (NR), trimipramine (0.3), tulobuterol (1.18), valsartan (1.26), warfarin (0.60)	16,17,19,20,23 27,28,29,31,33 34,36,37,41,44 60,62,77,79,86 87
HP-γ-CD	chloroquine (NR), iodiconazole (2.69), iodiconazole (1.26), mefloquine (0.84), methoxytolterodine (NR), primaquine (3.24), quinacrine (NR), quinocide (NR), tafenoquine (NR), tolterodine (NR)	16,23,33,79
HS-β-CD	bupropion (8.8), dimethindene (21.5), ephedrine (R), fluoxetine (11.1), nomifensine (34.1), orphenadrine (6.3), promethazine (6.4), propranolol (R), terfenadine (< 1.5), viloxazine (2.8)	70,71,73
HS-γ-CD	1-(3,4-dimethylphenyl)-2-(methylamino)propan-1-one (R), 4-fluoromethcathinone (R), amphetamine (R), amphetamine (R), buphedrone (NR), dimethylamphetamine (R), dimethylcathinone (NR), ephedrine (R), ephedrine (R), ethcathinone (NR), ethylone (R), ketamine (R), ketamine (R), ketamine (R), 1-(Benzo[d][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one (R), mephedrone (R), methamphetamine (R), methamphetamine (R), methedrone (R), methylenedioxyamphetamine (R), methylenedioxyethylamphetamine (R), methylenedioxymethamphetamine (R), methylephedrine (R), methylone (R), norephedrine (R), norephedrine (R), norketamine (R), norketamine (R), norketamine (R), norpseudoephedrine (R), norpseudoephedrine (R), pentedrone (NR), pentylone (R), pseudoephedrine (R), pseudoephedrine (R)	38,64,65,90,91 92
M-β-CD	atenolol (NR), bisoprolol (NR), duloxetine (NR), esmolol (NR), metoprolol (NR), naproxen (0.52), pranoprofen (< 0.40), propranolol (NR), repaglinide (NR), ritodrine (NR), sibutramine (1.3), sibutramine (1.48), sibutramine (1.3), valsartan (2.95), warfarin (NR)	18,30,34,41,60 61,75,86

M-γ-CD	duloxetine (> 1), duloxetine (NR), duloxetine (1.6)	77,86
P-α-CD	methoxytolterodine (NR), tolterodine (NR)	23
P-β-CD	methoxytolterodine (NR), tolterodine (NR)	23
P-γ-CD	methoxytolterodine (3.0), tolterodine (4.0)	23
PIP-β-CD	meptazinol (0.80)	54
RAMEB	amlodipine (2.48), carvedilol (1.98), chloroquine (NR), mefloquine (2.05), primaquine (NR), quinacrine (NR), quinocide (NR), sotalol (1.39), tafenoquine (NR)	16,27,28,31
S-α-CD	bupropion (> 3), chloroquine (NR), mefloquine (1.65), methoxytolterodine (2.0), ornidazole (R), primaquine (2.38), quinacrine (1.36), quinocide (NR), tafenoquine (NR), tolterodine (3.0	16,21,23,84
S-β-CD	2, 5-dimethoxy-4-bromoamphetamine (9.3), 2,3,4-trimethoxyamphetamine (1.4), 2,4,5-trimethoxyamphetamine (1.3), 2,4,6-trimethoxyamphetamine (2.5), 2,5-dimethoxy-4-chloroamphetamine (5.5), 2,5-dimethoxy-4-ethylamphetamine (2.6), 2,5-dimethoxy-4-iodoamphetamine (1.9), 2,5-dimethoxy-4-methylamphetamine (6.0), 2,5-dimethoxy-4-nitroamphetamine (1.1), 2,5-dimethoxy-4-propylamphetamine (2.8), 3,4,5-trimethoxyamphetamine (1.1), 3,4-dimethylmethcathinone (4.8), 3-fluoromethcathinone (1.9), 4-bromomethcathinone (0.9), 4-fluoromethcathinone (0.8), 4-methylethcathinone (2.7), α-pyrrolidinopropiophenone (2.1), amphetamine (> 3), buphedrone (1.2), butylone (2.3), cathinone (0.9), cetirizine (1.52), cetirizine (> 3), chloroquine (R), chloroquine (3.61), ethcathinone (1.3), ethylbuphedrone (1.8), ethylone (1.4), fluoxetine (R), hydroxyzine (1.76), isradipine (NR), ketamine (R), ketamine (R), ketamine (R), ketamine (R), mefloquine (9.85), mephedrone (2.3), meptazinol (NR), methcathinone (0.9), methedrone (0.0), methoxyamphetamine (1.5), methoxymethamphetamine (2.2), methoxytolterodine (11.0), methylendioxypyrovalerone (1.0), methylone (1.6), naphyrone (2.6), norketamine (R), norketamine (R), norketamine (R), norketamine (R), ofloxacin (5.45), ornidazole (R), ornidazole (6.28), pentedrone (2.9), primaquine (0.86), quinacrine (NR), quinocide (0.68), tafenoquine (NR), tolterodine (13.0)	15,16,17,21,22 23,24,32,35,42 45,52,81,89,90 93,94
S-γ-CD	chloroquine (0.85), mefloquine (1.90), primaquine (8.09), quinacrine (0.69), quinocide (NR), tafenoquine (NR)	16
SBE-α-CD	chloroquine (1.06), mefloquine (1.18), primaquine (1.07), quinacrine (1.41), quinocide (NR), tafenoquine (0.77)	16
SBE-β-CD	amlodipine (2.59), amphetamine (R), bupivacaine (R), carvedilol (1.03), chloroquine (R), chloroquine (0.5), isradipine (> 6), mefloquine (1.70), ornidazole (R), primaquine (5.87), quinacrine (2.26), quinocide (NR), repaglinide (R), sotalol (0.70), tafenoquine (NR)	16,27,28,32,52 20,21,30,31,81
SBE-γ-CD	chloroquine (NR), mefloquine (5.55), primaquine (8.36), quinacrine (NR), quinocide (NR), tafenoquine (NR)	16
SP-β-CD	ornidazole (R)	21
Succ-β-CD	chloroquine (1.08), mefloquine (1.35), primaquine (0.68), quinacrine (NR), quinocide (1.07), tafenoquine (NR)	16
Succ-γ-CD	carnitine (≈ 3)	85
TA-β-CD	duloxetine (NR)	86
TA-γ-CD	duloxetine (NR)	86
TM-α-CD	ketoprofen (1.30)	76
TM-β-CD	duloxetine (NR), iodiconazole (R), bambuterol (NR), chloroquine (NR), clenbuterol (NR), ephedrine (R), fenoterol (R), iodiconazole (0.67), ketoconazole (R), ketoprofen (1.70), mefloquine (NR), norephedrine (R), primaquine (1.03), procaterol (NR), propranolol (R), quinacrine (NR), quinocide (NR), salbutamol (NR), tafenoquine (0.68), talinolol (NR), tulobuterol (0.61)	16,19,29,33,43 67,71,73,74,76 79,86

TM-γ-CD	ketoprofen (2.50)	76

Table 2.- Comparison of the best enantioresolution reported for chiral drugs using neutral and anionic β-CDs (**NR:** unresolved, **R:** partially or totally resolved).

Drug	**Neutral β-CDs (Resolution)**	**Anionic β-CDs (Resolution)**	**Ref.**
1-(4-methoxyphenyl)-2-(methylamine)ethanol	β-CD (NR)	CM-β-CD* (R)	26
2-amino-1-phenyl-ethanol	β-CD (NR)	CM-β-CD (R)	26
4-fluoromethcathinone	β-CD (NR)	S-β-CD (0.8)	17,38
amlodipine	β-CD (0.86), RAMEB (2.48), HP-β-CD (2.33), CM-β-CD (9.8)	SBE-β-CD (2.59)	27,39,62
atenolol	M-β-CD (NR)	CM-β-CD (R)	61,69
butylone	β-CD (NR), HP-β-CD (NR)	CM-β-CD (0.39, S-β-CD (2.3)	17
carvedilol	β-CD (2.74), RAMEB (1.98), HP-β-CD (2.54), CM-β-CD (4.0)	SBE-β-CD (1.03)	28,40
cetirizine	β-CD (NR), HP-β-CD (NR)	S-β-CD (> 3)	35,62
chloroquine	β-CD (NR), RAMEB (NR), TM-β-CD (NR), HP-β-CD (NR), CM-β-CD (1.09), CE-β-CD (NR), Succ-β-CD (1.08)	S-β-CD (3.61), SBE-β-CD (R)	16,81
mefloquine	β-CD (0.30), RAMEB (2.05), TM-β-CD (NR), HP-β-CD (2.34), CM-β-CD (6.24), CE-β-CD (1.53), Succ-β-CD (1.35)	S-β-CD (9.85), SBE-β-CD (1.70)	16
mephedrone	β-CD (NR), HP-β-CD (NR), CM-β-CD (NR)	S-β-CD (2.3)	17
methoxytolterodine	β-CD (NR), DM-β-CD (NR), HE-β-CD (NR), HP-β-CD (NR), CM-β-CD (NR)	S-β-CD (11.0), P-β-CD (NR)	23
metoprolol	M-β-CD (NR)	CM-β-CD (R)	61,69
naphyrone	β-CD (NR), HP-β-CD (NR), CM-β-CD (1.9)	S-β-CD (2.6)	17
ofloxacin	β-CD (NR), HP-β-CD (R)	S-β-CD (5.45)	15,44
ornidazole	β-CD (NR), CE-β-CD (NR)	S-β-CD (6.28), SBE-β-CD (R)	15,21
primaquine	β-CD (NR), RAMEB (NR), TM-β-CD (1.03), HP-β-CD (NR), CM-β-CD (2.05), CE-β-CD (NR), Succ-β-CD (0.68)	S-β-CD (0.86), SBE-β-CD (5.87)	16
promethazine	β-CD (1.15)	HS-β-CD (6.4)	58,70
quinacrine	β-CD (NR), RAMEB (NR), TM-β-CD (NR), HP-β-CD (NR), CM-β-CD (1.67), CE-β-CD (NR), Succ-β-CD (NR)	S-β-CD (NR), SBE-β-CD (2.26)	16
quinocide	β-CD (NR), RAMEB (NR), TM-β-CD (NR), HP-β-CD (0.95), CM-β-CD (2.51), CE-β-CD (0.95), Succ-β-CD (1.07)	S-β-CD (0.68), SBE-β-CD (NR)	16
salbutamol	β-CD (NR)	CM-β-CD (R)	19,26

sibutramine	β-CD (1.1), M-β-CD (1.48), HP-β-CD (0.9), A-β-CD (2.86)	CM-β-CD (1.6)	18,41,75
sotalol	β-CD (NR), RAMEB (1.39), HP-β-CD (0.73), CM-β-CD (NR)	CM-β-CD (R), SBE-β-CD (0.70)	26,31
tafenoquine	β-CD (NR), RAMEB (NR), TM-β-CD (0.68), HP-β-CD (NR), CM-β-CD (1.44), CE-β-CD (NR), Succ-β-CD (NR)	S-β-CD (NR), SBE-β-CD (NR)	16
tolterodine	β-CD (NR), DM-β-CD (NR), HE-β-CD (NR), HP-β-CD (NR), CM-β-CD (NR)	S-β-CD (13.0), P-β-CD (NR)	23

*Depending on the pH of the BGE, CM-, CE- and Succ-CDs may be uncharged.

Table 3.- Dual chiral systems employed in chiral CE for the enantiomeric separation of drugs (**NR:** not resolved, **R:** partially or totally resolved).

Chiral selectors	Drug (Resolution)	Ref.
SBE-β-CD + S-β-CD	amphetamine (R)	52
β-CD + CM-β-CD CM-β-CD + HP-β-CD	desmethylzopiclone (> 2), zopiclone (> 2), zopicloneoxide (> 2) desmethylzopiclone (> 2), zopiclone (> 2), zopicloneoxide (> 2)	25
HS-β-CD + α-CD HS-β-CD + γ-CD HS-β-CD + HP-α-CD HS-α-CD + HP-γ-CD	tetrahydronaphthalenic derivatives (R) tetrahydronaphthalenic derivatives (R) tetrahydronaphthalenic derivatives (R) tetrahydronaphthalenic derivatives (R)	53
β-CD + PIP-β-CD HP-β-CD + PIP-β-CD PIP-β-CD + TM-β-CD	meptazinol (1.11) meptazinol (2.21) meptazinol (1.15)	54
DM-β-CD + TM-β-CD	oxprenolol (0.9), pindolol (1.4), propranolol (1.1)	55
β-CD + DM-β-CD	amphetamine (R), dimethylamphetamine (R), ephedrine (R), hydroxymethamphetamine (R), methamphetamine (R), methylenedioxyamphetamine (R), methylenedioxyethylamphetamine (R), methylenedioxymethamphetamine (R), methylephedrine (R), norephedrine (R),	56
HP-β-CD + [EMIm][L-lactate]	amlodipine (4.35), brompheniramine (2.76), chlorpheniramine (2.88), dioxopromethazine (1.85), homatropine (2.98), isoprenaline (2.48), liarozole (1.43), ofloxacin (5.35), propranolol (1.76), tropicamide (5.45)	57
β-CD + [EMIm][L-lactate] β-CD + [EMIm]Br	brompheniramine (4.52), carvedilol (3.50), chlorphenamine (3.04), dioxopromethazine (1.57), homatropine (1.63), homatropine (3.06), liarozole (2.62), promethazine (1.98), repaglinide (2.13), sibutramine (1.44), venlafaxine (1.26), zopiclone (5.20) brompheniramine (3.57), carvedilol (2.3), chlorphenamine (2.48), dioxopromethazine (1.19), homatropine (1.54), homatropine (2.99), liarozole (1.55), promethazine (1.41), repaglinide (1.28), sibutramine (1.24), venlafaxine (0.92), zopiclone (3.17)	58
HP-β-CD + DTAC	econazole (3.5), itraconazole (2.5), ketoconazole (2.8), miconazole (3.8)	59
Glu-β-CD + L-AlaC_4NTf_2 HP-β-CD + L-AlaC_4NTf_2 M-β-CD + L-AlaC_4NTf_2 Glu-β-CD + L-ValC_4NTf_2 HP-β-CD + L-ValC_4NTf_2 M-β-CD + L-ValC_4NTf_2	naproxen (2.58), pranoprofen (0.50), warfarin (0.63) naproxen (3.80), pranoprofen (0.60), warfarin (0.67) naproxen (1.56), pranoprofen (1.68), warfarin (0.50) naproxen (1.95), pranoprofen (0.90), warfarin (0.67) naproxen (3.28), pranoprofen (0.58), warfarin (0.85) naproxen (1.51), pranoprofen (1.40), warfarin (0.50)	60
M-β-CD + clarithromycin Glu-β-CD + clarithromycin HE-β-CD + clarithromycin HP-β-CD + clarithromycin	atenolol (1.77), bisoprolol (1.88), esmolol (1.75), metoprolol (2.10), nefopam (1.49), propranolol (1.70), ritodrine (1.33) nefopam (3.58) nefopam (2.72) nefopam (1.42)	61

β-CD + glycogen HP-β-CD + glycogen	amlodipine (NR), cetirizine (NR), citalopram (NR), duloxetine (NR), nefopam (NR) amlodipine (1.97), cetirizine (NR), citalopram (NR), duloxetine (0.42), nefopam (NR)	62
HS-γ-CD + (+)-18-C-6-TCA	3-fluoromethcathinone (R), 4-fluoromethcathinone (R), 4-methylethcathinone (R), amphetamine (R), methamphetamine (R), methylone (R), pentedrone (R), pentylone (R)	63

[EMIm][L-lactate]: 1-ethyl-3-methylimidazolium-L-lactate; **[EMIm]Br:** 1-ethyl-3-methylimidazolium-Br; **DTAC:** trimethyl ammonium chloride; **L-AlaC$_4$NTf$_2$:** L-alanine tert butyl ester bis (trifluoromethane) sulfonimide; **L-ValC$_4$NTf$_2$:** L-valine tert butyl ester bis (trifluoromethane) sulfonamide; **(+)-18-C-6-TCA:** (+)-18-crown-6-tetracarboxylic acid

Table 4.- LODs obtained for different drugs in chiral CE with different detection systems and preconcentration techniques.

CD	Drug (LOD µg/mL)	Detection	Precon. Tech.	Ref.
S-β-CD	ofloxacin (0.46), ornidazole (0.54)	UV-vis (230 nm)		15
HP-γ-CD	iodiconazole (4.6)	UV-vis (200 nm)		33
CM-β-CD	meptazinol (2.5)	UV-vis (237 nm)		24
RAMEB	sotalol (1.13)	UV-vis (232 nm)		31
RAMEB	amlodipine (2.31)	UV-vis (238 nm)		27
β-CD	carvedilol (1.13)	UV-vis (242 nm)		28
M-β-CD	sibutramine (0.25)	UV-vis (225 nm)		75
SBE-β-CD	isradipine (2.16)	UV-vis (239 nm)		32
CM-β-CD	zopiclone (0.01)	UV-vis (200 nm)		80
SBE-β-CD	chloroquine (0.6)	UV-vis (225 nm)		81
S-β-CD	cetirizine (0.075)	UV-vis (195 nm)		35
S-α-CD	ornidazole (0.3)	UV-vis (277 nm)		21
P-γ-CD	tolterodine (0.33)	UV-vis (200 nm)		23
CM-β-CD	amlodipine (1.0)	UV-vis (237 nm)		39
A-β-CD	valsartan (0.1)	UV-vis		34
HP-β-CD+[EMIm][L-lactate]	ofloxacin (0.53)	UV-vis		57
β-CD + [EMIm][L-lactate]	zopiclone (0.3)	UV-vis		58
S-α-CD	bupropion (0.048)	phosphorescence		84
SBE-β-CD	bupivacaine (0.052)	conductivity		20
CM-β-CD	anisodamine (0.18), atenolol (0.15), metoprolol (0.08)	ECL		69
Succ-γ-CD	carnitine (0.01)	IT-MS		85
HS-γ-CD	4-fluoromethcathinone ($1.2x10^{-3}$), dimethylcathinone (0.011), ethcathinone ($1.0x10^{-3}$), buphedrone ($3.5x10^{-3}$), pentedrone ($3.7x10^{-3}$), methedrone ($5.0x10^{-3}$), methylone ($9.5x10^{-3}$), mephedrone ($5.0x10^{-3}$), ethylone ($3.8x10^{-3}$), 1-(3,4-dimethylphenyl)-2-(methylamino)propan-1-one ($5.0x10^{-3}$), Pentylone ($6.7x10^{-3}$), 1-(Benzo[d][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one ($5.5x10^{-3}$)	TOF-MS		38

HP-β-CD	duloxetine (0.02), duloxetine (0.2)	IT-MS		86
α-CD	trimipramine ($7x10^{-3}$)	UV-vis (214 nm)	EME	36
HP-β-CD	amlodipine ($3x10^{-3}$)	UV-vis (214 nm)	EME	87
HP-β-CD	propranolol ($7x10^{-3}$)	UV-vis (214 nm)	EME	37
β-CD	methamphetamine ($0.2x10^{-3}$), methylenedioxymethamphetamine ($0.08x10^{-3}$), ketamine ($0.15x10^{-3}$)	UV-vis (200 nm)	DLLME	88
S-β-CD	cetirizine (0.037), hydroxyzine (0.075)	UV-vis (214 nm)	DLLME	22
CM-β-CD	zopiclone ($0.27x10^{-3}$), desmethylzopiclone ($0.15x10^{-3}$)	UV-vis (310 nm)	DLLME	25
CM-β-CD	carvedilol ($4x10^{-3}$)	UV-vis (241 nm)	DLLME + FASI	40
DM-β-CD + TM-β-CD	pindolol ($2.5x10^{-5}$), oxprenolol ($1.1x10^{-4}$), propranolol ($2.6x10^{-5}$)	UV-vis (220 nm)	FASI	55
HS-γ-CD	norketamine (0.18)	UV-vis (195 nm)		92
S-β-CD	ketamine (0.02), norketamine (0.02)	UV-vis (200 nm)		93
S-β-CD	ketamine ($8x10^{-3}$), norketamine ($8x10^{-3}$)	UV-vis (195 nm)		94