Sulfobutylether Beta-Cyclodextrin as Chiral Selector in Capillary Electrophoresis

Cyclodextrins (CDs) are the most frequently used chiral selectors in the capillary electrophoresis [1]. For academic research usually single isomer CDs are used, but for practical purposes the random substituted CDs give often suitable results especially when CD derivatives produced industrially are used. Sulfobutylether beta-CD (SBE-β-CD) is a pharmaceutical excipient in US Pharmacopoeia as solubilizing agent [2] and is a component of several drug formulations in the market. Its composition is strictly regulated therefore the average degree of substitution (DS) and the distribution of the components of various DS fall always in a narrow range. The standard quality results in high reproducibility for analytical applications.

The first report on the application of SBE-β-CD in capillary electrophoresis (CE) was published in 1994 by the group of Valentino Stella [3]. In this pioneering work, the authors demonstrated that enhanced enantiomeric separation can be achieved when the electrophoretic mobility of the chiral selector is opposite to that of the analyte. The “extended” enantiorecognition ability of SBE-CDs, based on the advantage of the countercurrent flow of the negatively charged additive with respect to the electroosmotic flow (EOF), was then further deepened by other scientists. Along the years, the family of sulfobutylated CDs gained popularity and SBE-β-CD is often referred as the most versatile chiral additive among the negatively charged CDs (and CDs in general) as it allows the enantioseparation of a wide variety of pharmacologically active racemates.

The use of SBE-CDs in CE is suitable for the analysis of illicit amphetamine, methamphetamine, methcathinone and propoxyphene [4] and for the enantiomeric separation of ephedrine and related compounds [5]. Chankvetadze et al. described the use of SBE-β-CD as a chiral additive for the resolution of basic racemic drugs, such as clenbuterol, dimethindene, etilefrine, mefloquine and metomidate, in free capillary zone electrophoresis.
The resolution of the racemates was achieved with very low concentrations (micromolar) of the chiral additive and the high efficiency of the selector was attributed to its counter-current mobility in respect to the racemic solute [6].

Also Desiderio and Fanali reported on the effective use of SBE-β-CD as a chiral selector in CE in a study on the enantiomeric separation of warfarin, pindolol, propranolol, terbutaline, etc., a variety of underivatized anionic and cationic compounds of pharmaceutical interest as well as dansyl-amino acids [7].

SBE-β-CD was found as best chiral selector for the enantiomeric separation of several neutral and anionic herbicides by capillary zone electrophoresis [7]. SBE-γ-CD has been also investigated as chiral selector for CE. A comparative study between SBE-γ-CD and native γ-CD has shown that SBE-γ-CD is more efficient in the electrophoretic separation of cationic analytes, but it cannot generally replace γ-CD since the enantioselectivities of the two selectors are sometimes distinctly different [8]. Electrophoretic chiral separation of chloroquine and pemoline was effectively achieved by using 2.5 mM SBE-β-CD and 1.0 mM SBE-β-CD in 50 mM pH 2.5 sodium phosphate buffer, respectively [9]. Fundamental drugs used for the clinical treatment of Parkinson's disease, such as DOPA and structurally related compounds were resolved into their enantiomers by CE with SBE-β-CD as chiral selector [10–11]. The use of SBE-β-CD as chiral additive in CE was also useful for the separation of estrogens and amino acid derivatives [12–14]. The enantioseparations of the antimalarian erythro-mefloquine and its analogues were screened by CE using library of CD derivatives, including SBE-β-CD, as chiral selectors [15].

The chiral separation of the dihydropyridine calcium channel blockers (DHPs) with CE has been reported utilizing SBE-β-CD as the chiral selectors: it was found that the anionic SBE-β-CD gives a robust separation of amlodipine enantiomers when using acetonitrile - 20 mM NaH₂PO₄ (pH 3.95), containing 20 mM SBE-β-CD (35:100, v/v) [16]. Kong et al. developed an electrophoretic method for the enantioseparation of neutral m-nisoldipine, by comparing SBE-β-CD and carboxymethyl-β-CD (CM-β-CD) as chiral selectors. It was concluded that SBE-β-CD was superior chiral selector than CM-β-CD. It was also pointed out that the DS of the SBE-β-CD can remarkably influence the enantiorecognition process. In particular, high DS SBE-β-CD induced better investigated by CD-mediated CE and it was found that the enantiomers of the neutral dihydropyridines were baseline-separated only with SBE-β-CD [18].

Fillet et al. performed comparative chiral resolution studies among the commonly used neutral CDs with SBE-β-CD. Increased enantiomeric resolution for various acidic drugs was achieved by using dual systems comprising neutral β-CD and charged SBE-β-CD [19].

The extensive work on the use of anionic CDs in chiral CE have been summarized in excellent reviews [20–22]. De Boer et al. in their review reported several examples about the utility of sulfobutylated β- and γ-CDs as chiral selectors and the authors referred to SBE-β-CD.
as the “most widely used anionic CD derivative” [23]. In the review by Mikuš et al. [24], some new achievements in the use of SBE-CDs are reported.

Further papers on the analytical application of SBE-CDs are summarized in Table 1.

**Table 1. Examples of using SBE-β-CD as chiral selector**

<table>
<thead>
<tr>
<th>Analytes</th>
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<tr>
<td>tadalafil</td>
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<td>imperanene</td>
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<td>isradipine enantiomers</td>
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<td>chloroquine enantiomers</td>
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<td>benzofurys, cathinones, diphenidines, ethylphenidate, methiopropamine and thiothione</td>
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<tr>
<td>brompheniramine, chlorpheniramine, cetirizine and promethazine racemate</td>
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<td>pantoprazole enantiomers</td>
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</tbody>
</table>

a SBE-α-CD, b SBE-β-CD (average DS ~4), c SBE-γ-CD (DS ~4), d SBE-β-CD and native β-CD dual CD system, e electrokinetic chromatography (EKC)

The versatility of SBE-CDs as capillary electrophoretic tools, together with their commercial availability largely justify the extensive research conducted so far on this family of derivatives. The large number and wide structural variety of guest molecules where efficient chiral resolution was achieved demonstrate not only the excellent enantiorecognition but also the general and high affinity complex forming ability of these cyclodextrin derivatives.
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Toward Successful Cyclodextrin Based Solubility-Enabling Formulations for Oral Delivery of Lipophilic Drugs: Solubility-Permeability Trade-Off, Biorelevant Dissolution, and the Unstirred Water Layer

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*Active targeting hepatocytes with β-CD, Decreasing the concentration of intracellular cholesterol, Negligible cytotoxicity, Increased internalization*


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