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Separation of chiral drugs with sulfobutylether-β-cyclodextrin by capillary zone electrophoresis

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Abstract: Sulfobutylether-β-cyclodextrin (SBE-β-CD) was used as a chiral selector for separating ten chiral drugs with resolution ≥ 1.2 by capillary zone electrophoresis (CZE). The background electrolyte solution comprised of 120 mmol/L Britton-Robinson buffer (BRB) containing 1~10 mmol/L SBE-β-CD with the pH value adjusted from 5.0~6.8. Five of the drugs were better resolved than those previously reported with neutral CDs.

Keywords: Chiral separation; sulfobutylether-β-cyclodextrin; capillary zone electrophoresis; anisodamine; bencynonate: econazole; esmolol; glycopynonate; lobeline; methoxamine; phenylephrine; pinacidil; terazosin.

Introduction

Charged cyclodextrins were first introduced by Terabe[1] for chiral separation of amino acids, and the charged CD commonly used nowdays are carboxymethyl-β-CD (CM-β-CD), β-CD-phosphate, γ-CD-phosphate, sulfobutylether-β-cyclodextrin (SBE-β-CD) etc. Compared with neutral CDs the charged CDs have better solubility in aqueous solution and wider pH range for use. Among the negatively charged CDs, SBE-β-CD is one of the most popular one used with great success rate, suitable to be used in the pH range from 2.5 to 9.0. In the present communication, ten chiral drugs separated previously with neutral cylcodextrins were further separated by SBE-β-CD with a result of half of them being better resolved.

Experimental

All the chiral drugs were provided by National Institute for the Control of Pharmaceuticals and Biological Products (Beijing, P. R. China). SBE-β-CD was donated by Bioscience Innovations, USA with a concentration of 50mmol/L and DS (degree of substitution) 4.0. All other chemicals were of analytical grade. 120mmol/L Britton-Robinson buffer (BRB) solution was prepared according to reference[2] and subjected to filtration with 0.45μm

membrane and degassing with sonication prior to use. The background electrolyte (BGE) solution was prepared by diluting a calculated amount of the original 50mmol/L SBE-β-CD solution with 120mmol/L BRB solution. For separating the drugs 10mmol/L, 5mmol/L, 1mmol/L SBE-β-CD in BRB solution were used and precise pH test paper was used for monitoring the pH value of the BGE.

Approximate 1 mg/ml solution of each drug (anisodamine, bencynonate, econazole, esmolol, glycopynonate, lobeline, methoxamine, phenylephrine, pinacidil, terazosin) were prepared with BRB solution. Before injection further dilution was needed.

Experiments were carried out on a HP-CE^{3D} system with a DAD. A fused silica capillary (Yongnian Optical Fiber Factory, Hebei) was used as the separation tube. On-column detection was performed at the cathode on at 214 nm and 254 nm dual wavelength. The CE operation conditions are mentioned in **Table 1**. Samples were injected with pressure mode at anode. Before each run 1mol/L NaOH, re-distilled water and the BGE solution were used consecutively to rinse the column for 2 min each.

Results and Discussion

Preliminary tests revealed that the concentration of the chiral selector SBE-β-CD should be chosen between 1 mmol/L and 10 mmol/L. At 5 mmol/L SBE-β-CD five of them were well resolved, for the other five drugs either 1 mmol/L SBE-β-CD or 10 mmol/L SBE-β-CD is necessary to improve the resolution.

Besides, the pH optimization was effective in enhancing the resolution. For bencynonate, esmolol, phenylephrine, terazosin, the pH value of the BGE should be somewhat increased.

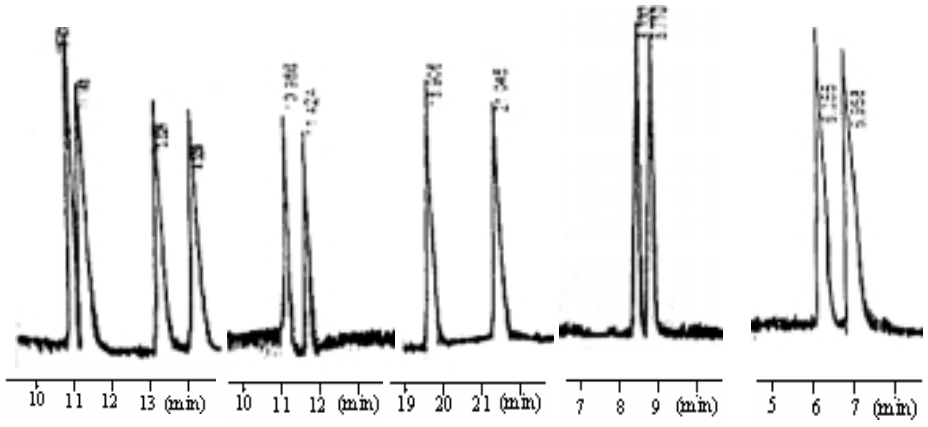
Furthermore, sample amount reduction also proved to be effective in enhancing the resolution. For example the resolution of anisodamine, glycopynolate, methoxamine, phenylephrine, pinacidil and terazosin were all improved considerably by reducing the injection amount through reducing either the sample concentration or the injection time or both of them simultaneously.

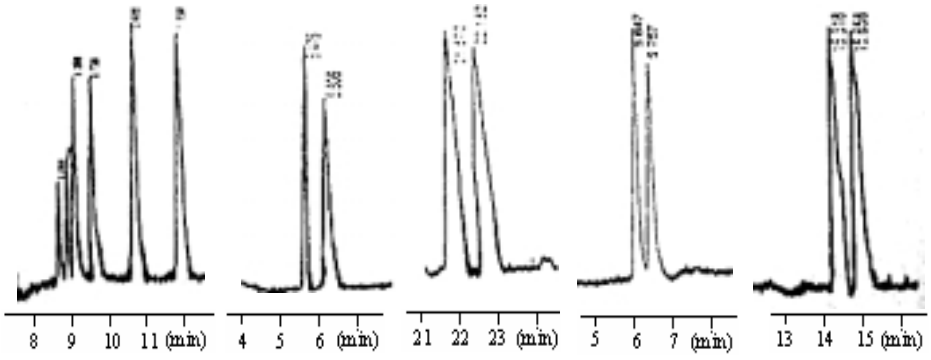
It is worthwhile to mention that the solid sample was dissolved in the BRB solution, giving satisfactory peak shapes as shown in the electropherograms under **Table 1**. of the ten drugs separated five of them were resolved with better resolution than those previously separated with neutral CDs. The most striking example is that obtained for lobeline which contains three asymmetric carbon atoms in the molecule, giving theoretically four pairs of peaks. Wang *et al.* obtained two pairs of peaks, one being only partially resolved. With SBE-β-CD used in the work, three pairs of baseline resolved pairs of peaks were obtained. The higher success rate of chiral separation with SBE-β-CD as selector might be attributed to the multiplicity of its structure, i.e., SBE-β-CD is actually a mixture of complex composition with various degree of substitution and a host of positional isomers[11].

Table 1. Separation condition for resolving chiral drugs with SBE-β-CD as selector

Drug name	Discrepancies from the standard conditions	R_s	R_s in the literature
Anisodamine	1mmol/L CS, 6s	1.2, 2.0	0.97[3]
Bencynonate	pH=6.0	2.8	3.1[4]
Econazole	1mmol/L CS	5.2	2.0[4]
Esmolol	pH=6.7, 25kV, 25℃	1.5	3.1[5]
Glycopynolate	1mmol/L CS, pH=6.0, 6s	1.8	0.5, 0.7[3]
Lobeline	10mmol/L CS	1.8, 4.5, 4.8	0.6, 1.5[6]
Methoxamine	3s	3.3	1.4[6-8]
Phenylephrine	pH=6.0, 0.3mg/ml, 3s	1.6	4.2[9]
Pinacidil	3s	1.2	2.2[10]
Terazosin	pH=6.0, 0.25mg/ml, 3s	1.8	1.2[5]

Standard conditions: 50 cm (41.5 cm effective length)×50 μm I.D. fused silica capillary column; applied voltage, 20 kV; temperature, 20℃; hydrostatic injection, 5 kPa with 10s injection time; selector concentration, 5mmol/L SBE-β-CD (CS); buffer solution, 120 mmol/L BRB, pH=5.0; sample concentration, 0.5 mg/ml in BRB.





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