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Chiral separation by counter-current chromatography

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ABSTRACT

Counter-current chromatography (CCC) is a new, efficient, productive chromatographic technique based on continuous liquid-liquid partition. Recently, it attracted more attention in chiral separation due to its high load capacity, cheap liquid stationary phase and low solvent consumption, when compared to traditional chiral separation techniques. This review presents advances and applications of chiral separation using high-speed CCC in recent years. We summarize the major benefits and the limitations of chiral separation by CCC. We introduce in detail some novel methods, which can improve the resolution of enantiomers and are easily achieved on classical CCC apparatus. We also outline challenges and future perspectives in developing chiral separation by CCC.

Contents

1. Introduction

Chiral separation is the main method to obtain individual enantiomers. Counter-current chromatography (CCC) processes are powerful preparative techniques due to their high capacity and low cost of solvent. They can achieve chiral separation through establishing a chiral environment by adding a chiral selector.

According to the literature, the first attempt at chiral separation with CCC was by Prelog's group [1]. They selected (R,R)-di-5-nonyltartrate as a chiral selector and employed a rotation locular CCC machine and a 1,2-dichloroethane-water solvent system to achieve chiral separation of racemic norephedrine. Although this experiment accomplished a partial separation, it still got high-purity enantiomers and proved that the CCC technique can be used in chiral separation.

However, because of the low theoretical plates of CCC and the absence of highly selective chiral selectors, chiral CCC is developing slowly and is not as popular as other technologies, such as high-performance liquid chromatography (HPLC) and capillary electrophoresis (CE).

Foucault [2] specifically reviewed the progress of chiral separation by CCC and centrifugal partition chromatography in 2001. Some other reviews [3–5] also mentioned chiral separation by CCC.

Abbreviations: 2-PPA, 2-phenylpropionic acid; BCR, Biphasic chiral recognition; BRCE, Biphasic recognition chiral extraction; CCC, Counter-current chromatography; CE, Capillary electrophoresis; ChMWat, Chloroform/methanol/water; EbuWat, Ethyl acetate/butanol/water; GC, Gas chromatography; HEMWat, Hexane/ethyl acetate/methanol/water; HPCCC, High-performance counter-current chromatography; HPLC, High-performance liquid chromatography; HSCCC, High-speed counter-current chromatography; MDM, Multiple dual-mode elution; MTBE, Methyl t-butyl ether; NAP, 2-(6-methoxy-2-naphthyl)propionic acid; REM, Recycling elution mode.

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High-speed CCC (HSCCC) is a kind of CCC based on the hydrodynamic equilibrium system, which is designed using a J-type synchronous planetary motion to improve the separation efficiency. The higher retention of the stationary phase with higher flow rate was achieved by this system, rather than the I-type centrifuge and the locular CCC devices mentioned above, so this CCC system was named HSCCC.

Then, a novel J-type CCC device was developed with increased rotational speed and g-force field, which finally led to better stationary-phase retention, increased efficiency and shorter run times than the initial HSCCC, so this was named high-performance CCC (HPCCC). At present, HPCCC is a powerful and widely used instrument because of its higher separation efficiency and shorter separation time than other CCC systems.

In recent years, studies on chiral separation by CCC aroused considerable interest among researchers and a number of related articles were published. This review will give a brief summary of recent progress in research on applications of CCC to chiral separation, discuss the advantages and the disadvantages of the chiral separation by CCC, and highlight novel approaches and excellent examples of applications.

2. Application

Recently, chiral separation by CCC saw increased activity with an increase in the number of publications.

Table 1 is a brief summary of some relevant examples reported in the literature of applications of J-type CCC for chiral separation, which summarizes the solvent systems, chiral selectors and racemates in the applications, because the choices of solvent system and chiral selector are key factors that affect separation in a chiral separation by CCC. Table 1 classifies and analyzes the published articles and the results were shown in Figs. 1–3.

Figs. 1–3 show that the applications of J-type CCC to chiral separation have zoomed in the past five years. Publications in 2010–14 are the 4.67 times as many as in 2005–09.

β-cyclodextrin derivatives are the chiral selectors most widely used in CCC because of their high stereoselectivity and chiral recognition

Table 1
Chiral separations by J-type counter-current chromatography

Target racemate	Solvent system	Chiral selector	Ref.
N-(3,5-dinitrobenzoyl)-(±)-phenylglycine, N-(3,5-dinitrobenzoyl)-(±)-phenylalanine, N-(3,5-dinitrobenzoyl)-(±)-valine and N-(3,5-dinitrobenzoyl)-(±)-leucine	*N*-hexane/ethyl acetate/methanol/10 mm hydrochloric acid (8:2:5:5, v/v) *N*-hexane/ethyl acetate/methanol/10 mm hydrochloric acid (6:4:5:5, v/v) (for preparative separation of N-(3,5-dinitrobenzoyl)-(±)-leucine) and methyl *tert*-butyl ether/water (for pH-zone-refining CCC) [6]	N-dodecanoyl-L-proline-3,5-dimethylanilide	[6,7]
7-des-Methyl-ormeloxifene	Ethyl acetate/methanol/triethylammonium acetate buffer (10:3:7, v/v)	B-cyclodextrin	[8]
Gemifloxacin	*N*-butanol/ethyl-acetate/20 mm bis(2-hydroxyethyl)aminotris(hydroxymethyl) methane acetate buffer (6:5:10, v/v)	(+)-(18-crown-6)-tetracarboxylic acid	[9]
Chlorpheniramine	Ethyl acetate/methanol/water (10:1:9, v/v)	Carboxymethyl-β-cyclodextrin	[10]
A-methylbenzylamine	Chloroform/methanol/water (4:3:1, v/v)	L-(+)-tartaric acid	[11]
(±)-N-(3,4-cis-3-decyl-1,2,3,4-tetrahydrophenanthren-4-yl)-3,5-dinitrobenzamide and N-(3,5-dinitrobenzoyl)-(±)-leucine	**n*-hexane/ethyl acetate/methanol/water (9:1:9:1, v/v) and Methyl *tert*-butyl ether/50 mm phosphate buffer (pH 6.0)	N,N-diethyl-(S)-naproxenamide	[12]
A-cyclohexylmandelic	*N*-hexane/methyl tert-butyl ether/water (9:1:10, v/v)	(−)-2-ethylhexyl tartrate and hydroxypropyl-β-cyclodextrin were respectively employed as lipophilic and hydrophilic chiral selectors	[13]
N-(3,5-dinitrobenzoyl)-(±)-leucine and N-(3,5-dinitrobenzoyl)-tert-butyl-(±)-leucinamide	Ethoxynonafluorobutane/isopropanol/water (25:35:40, v/v)	N-perfluoroundecanoyl-L-proline-3,5-dimethylanilide	[14]
Lomefloxacin hydrochloride	Ethyl acetate/methanol/water (10:1:10, v/v)	Sulfated-β-cyclodextrin	[15]
Ofloxacin	Ethyl acetate/methanol/water (10:1:9, v/v)	L-(+)-tartaric acid	[16]
(R, S)-naproxen	*N*-hexane/ethyl acetate/0.1 mol l^{-1} phosphate buffer solution (pH 2.67) (8:2:10, v/v)	Hydroxypropyl-β-cyclodextrin	[17]
Phenylsuccinic acid	*N*-hexane/methyl *tert*-butyl ether/0.1 mol l^{-1} phosphate buffer solution (pH 2.51) (0.5:1.5:2, v/v)	Hydroxypropyl-β-cyclodextrin	[18]
Propranolol, pindolol and alprenolol	Chloroform/0.05 mol l^{-1} acetate buffer containing 0.10 mol l^{-1} boric acid (1:1, v/v)	Di-*n*-hexyl l-tartrate	[19]
2-phenylpropionic acid	*N*-hexane/ethyl acetate/0.1 mol l^{-1} phosphate buffer solution pH 2.67 (5:5:10 for isocratic elution and 8:2:10 for recycling elution, v/v)	Hydroxypropyl-β-cyclodextrin	[20]
Propafenone	Chloroform/0.05 mol l^{-1} acetate buffer pH 3.4 (1:1, v/v)	Di-*n*-butyl l-tartrate	[21]
2-(6-methoxy-2-naphthyl)propionic acid (NAP) and 2-phenylpropionic acid(2-PPA)	*N*-hexane/ethyl acetate/0.1 mol l^{-1} phosphate buffer pH 2.67 (7.5:2.5:10 for NAP and 7:3:10 for 2-PPA, v/v)	Hydroxypropyl-β-cyclodextrin	[22]
Trans-δ-viniferin	*N*-hexane/ethyl acetate/water (5:5:10, v/v)	Hydroxypropyl-β-cyclodextrin	[23]
Phenylsuccinic acid	*N*-hexane/methyl *tert*-butyl ether/water (0.5:1.5:2, v/v)	D-isobutyl tartrate and hydroxypropyl-β-cyclodextrin were respectively employed as lipophilic and hydrophilic chiral selectors	[24]
Aromatic α-hydroxyl acids	*N*-butanol/water (1:1, v/v) or hexane/*n*-butanol/water (0.5:0.5:1, v/v)	N-*n*-dodecyl-l-proline	[25]
Oxybutynin	N-hexane/methyl tert-butyl ether/0.1 mol l^{-1} phosphate buffer solution pH 5.0 (6:4:10, v/v)	Hydroxypropyl-β-cyclodextrin	[26]

* In this article, two different solvent systems were used to achieve the chiral separation of the two racemates, respectively: *n*-hexane/ethyl acetate/methanol/water for ((±)-N-(3,4-cis-3-decyl-1,2,3,4-tetrahydrophenanthren-4-yl)-3,5-dinitrobenzamide and methyl *t*-butyl ether (MTBE)/phosphate buffer for N-(3,5-dinitrobenzoyl)-(±)-leucine.