Journal of Chromatography A, xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Chromatography A

journal homepage: www.elsevier.com/locate/chroma

Review article

A review on chiral separation by counter-current chromatography: Development, applications and future outlook

Xin-Yi Huang[a,*], Dong Pei[a,b], Jian-Fei Liu[a], Duo-Long Di[a,b,*]

[a] CAS Key Laboratory of Chemistry of Northwestern Plant Resources and Key Laboratory for Natural Medicine of Gansu Province, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, China
[b] Center of Resource Chemical and New Material, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Qingdao, China

ARTICLE INFO

Article history:
Received 25 June 2017
Received in revised form 27 October 2017
Accepted 29 October 2017
Available online xxx

Keywords:
Chiral separation
High-speed counter current chromatography
Centrifugal partition chromatography

ABSTRACT

Chiral separation has been a remarkably active area of research over the past long time and it still stays that way. Over the last few decades, counter-current chromatography (CCC) was successfully applied to the field of chiral separation. It provides an attractive approach to obtain pure enantiomer, particularly in preparative application because of its unique advantages of high load capacity, low solvent consumption and easy scale-up. The last several years great strides have been made in chiral separation by CCC, ranging from novel elution modes such as recycling elution mode and multiple dual mode elution to more specialized approaches such as pH-zone-refining and biphasic chiral recognition technologies. These developments have greatly improved the resolution of enantiomers and promoted the application of CCC in the field of chiral separation. Although not as popular as its application to the field of separation of natural product, the development of chiral separation by CCC should not be underrated. In this review article, we refer to the development, applications and future outlook of chiral separation by CCC, with emphasis on topics of its history, mechanism, advantages, limitations, current development and challenges. Meanwhile, its orientation of continued evolution and future outlook also have been discussed. While some scientific and technological problems have not yet been solved thoroughly, chiral separation by CCC has demonstrated potential advantages and prospects in this field and has good chance at preparative enantioseparation.

Contents

Abbreviations: HSCCC, high-speed counter-current chromatography; CCC, counter-current chromatography; CPC, centrifugal partition chromatography; HPLC, high performance liquid chromatography; MP, mobile phase; SP, stationary phase; DM, dual-mode elution; MDM, multiple dual-mode elution; REM, recycling elution mode; CLR, closed-loop recycling elution mode; BCR, biphasic chiral recognition; HPCPC, high-performance centrifugal partition chromatography; HPCCC, high-performance counter-current chromatography.

* Corresponding authors at: CAS Key Laboratory of Chemistry of Northwestern Plant Resources and Key Laboratory for Natural Medicine of Gansu Province, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, China.
E-mail addresses: huangxy@licp.cas.cn (X.-Y. Huang), didl@licp.cs.cn (D.-L. Di).

https://doi.org/10.1016/j.chroma.2017.10.073
0021-9673/

1. Introduction

How to obtain pure enantiomer has long been an intriguing problem because the biological and pharmacological activity is usually restricted to one of the enantiomer. So far, chiral separation is proven and still is main method of getting pure enantiomer [1]. A tremendous amount of works have been done on the separation of enantiomers. Lots of novel technologies have been introduced and thousands of literatures are published and continuously increased, which illustrates the public has a high interest in this field [2–8]. However, chiral separation is still a challenge and how to get individual enantiomer remains a hot issue [9,10]. The demand for specialized chiral separation technology and continuous technological development is real [11,12]. Therefor it is important to exploit efficient and low-cost chiral separation technology.

Counter-current chromatography (CCC) is a chromatographic technique which is based on liquid–liquid partition principle [13,14]. It is an excellent preparative separation tool due to its high capacity, low solvent consumption and flexible elution modes [15–17]. So CCC has been widely used in the field of natural product chemistry and other fields since the time of its invention [18–21]. CCC can also achieve chiral separation through establishing chiral environment in the column by adding chiral selector to the stationary phase [22]. It provides an alternative approach to obtain individual enantiomer and has an immense potential in chiral separation, especially in preparative applications. With the development of the instrument and technology, chiral separation by CCC is assuming an increasing attention and plays a more and more active role in chiral separation. Especially since 2010, the development trend in this area is accelerating.

But, there are only two English reviews that focus on this topic were published in the past decades years. One is published in 2001 by Foucault [22] and the other is published in 2015 by our group [23]. The last review that we published has presented the advances and applications of chiral separation by high-speed CCC (HSCCC). It focuses the attention mainly on some novel methods and approaches which can improve the resolution of HSCCC enantioseparation and easily achieved on classical HSCCC apparatus. While in this review, we mainly introduce the history, mechanism, advantages, limitations, current development and challenges as well as the orientation of continued evolution and future outlook of chiral separation by CCC. Meanwhile, this review also shares our vision and ideas on how to meet the challenge and conquer the defect in chiral separation by CCC. We hope it can broaden professional interests of the readers which in related field and promote the development of this technique.

2. Chiral separation by CCC

2.1. The history of chiral separation by CCC

As recorded in the literature, the first and meaningful work of chiral separation by CCC was achieved by Hostettmann and co-workers in 1982 [24]. In their work, a rotation locular CCC was employed to separate racemic norephedrine with (*R, R*)-di-5-nonyltartrate as chiral selector. Despite partial separation of the racemate, this experiment still obtained high-purity individual enantiomer. Then, the second work to separate enantiomers with CCC was achieved by Tanimura's group in 1984 [25]. They carried out complete resolution of DL-isoleucine by employing a droplet CCC with the ligand copper complexes of copper (II) ion and *N*-dodecyl-L-proline as chiral selector. The third work in this area was described by Oya and Snyder in 1986 [26]. They fulfilled the resolution of different bicyclo [2.2.I] hept-5-ene-2-carboxylic acid derivatives by a droplet CCC with (−)-(*R*)-2-Aminobutanol as chiral selector. These primary attempts with early CCC instruments demanded a couple of days to achieve the full separation of enantiomers due to the poor efficiency, but they turned out that CCC technique can be used in chiral separation. Since these initial works in 1980s, Oliveros et al. [27] successfully completely resolved two racemic compounds, *N*-(3,5-dinitrobenzoyl)-*tert*-butylvallnamide and *N*-(3,5-dinitrobenzoyl)-*tert*-butylleucinamide by a centrifugal partition chromatography (CPC) apparatus with a column volume of 240 mL in dozens of minutes. CPC is a type of liquid–liquid chromatography based on hydrostatic equilibrium and this is the first speedy chiral separation with modern counter-current chromatography instrument. This experiment changes the original impression that CCC is time-consumption in chiral separation and it is a tribute to the application of CCC in this area. Then, Ito's group realized the chiral separation of several racemic dinitrobenzoyl amino acids by HSCCC [28] and gram quantities of racemates can be successfully separated in a single run using a HSCCC apparatus with a column volume of 330 mL in several hours [29]. Furthermore, the loading capacity can be further increased and the separation time can be further reduced through pH-zone-refining technique [29,30]. These modern CCC instruments, CPC and HSCCC are both running in a gravity field produced by the rapidly rotating rotor which is fitted with column. In contrast with early CCC instruments, this novel design remarkably improved separation efficiency in terms of resolution, separation time and sample loading capacity. These applications of modern CCC instruments in this area created a new situation in rapid preparative chiral separation. More and more researchers became interested in chiral separation by CCC and the related publications increase gradually and show a good momentum of accelerated growth [23].

2.2. The way to achieve chiral separation by CCC

In chiral separation by CCC, a suitable hydrophilic or lipophilic chiral selector is added to the aqueous or organic phase and usually the liquid phase dissolved chiral selector is used as stationary phase. First, the chiral stationary phase filled the column in order to provide an enantioselective environment in the column, then the mobile phase was pumped into the column while the column revolved with high speed. When the clear mobile phase appears at the outlet of the column, it indicates that the two phases in the column have reached equilibrium. Then the racemate solution was injected. The enantiomer has the priority to bind chiral selector will form complex derivative that exhibits different chromatographic behavior from the original. Therefore, by relying on the different affinities of dextrorotatory and levorotatory enantiomers for chiral selector, the racemate is resolved. The schematic diagram of this process can be seen in Fig. 1.

The mechanism of chiral separation by CCC was described here by means of a simplified mathematic model to help the users understand it [27,31]. First, suppose the chiral selector in the stationary phase and its complex derivative are not occurring in the mobile

Please cite this article in press as: X.-Y. Huang, et al., A review on chiral separation by counter-current chromatography: Development, applications and future outlook, J. Chromatogr. A (2017), https://doi.org/10.1016/j.chroma.2017.10.073