Journal of Chromatography A, xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Chromatography A

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

Advances in high-throughput and high-efficiency chiral liquid chromatographic separations

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ARTICLE INFO

Article history:
Received 13 May 2016
Received in revised form 13 July 2016
Accepted 15 July 2016
Available online xxx

Keywords:
High-efficiency chiral separations
High-throughput chromatography
Superficially porous particles
HPLC and SFC enantiomeric separations
Ultrafast separations
Instrument optimizations

ABSTRACT

The need for improved liquid chromatographic chiral separations has led to the advancement of chiral screening techniques as well as the development of new, high efficiency chiral separation methods and stationary phases. This review covers these advancements, which primarily occurred over the last 15 years. High throughput techniques include multi-column screening units, multiple injection sequences, and fast gradient SFC screening. New separation methods and column technologies that aim at high efficiency chiral separations include the use of achiral UHPLC (i.e. sub-2 μm) columns for separating derivatized chiral analytes or using chiral additives in the run buffer, UHPLC chiral stationary phases, and superficially porous particle based chiral stationary phases. Finally, the enhancement of chiral separations through these new technologies requires that certain instrumental considerations be made. Future directions in continuing to improve chiral separations are also discussed.

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http://dx.doi.org/10.1016/j.chroma.2016.07.040
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Please cite this article in press as: D.C. Patel, et al., Advances in high-throughput and high-efficiency chiral liquid chromatographic separations, J. Chromatogr. A (2016), http://dx.doi.org/10.1016/j.chroma.2016.07.040

1. Introduction

As chromatographic technology matures, the ability to perform difficult separations improves. Common improvements include increasing peak capacities and developing novel surface chemistries capable of separating structurally related molecules. It is of a great importance for researchers of novel chromatographic stationary phases to continue to advance the science, by developing new separation technologies, in order to keep pace with the ever-growing plethora of newly discovered chemical compounds. The most difficult chromatographic separations involve the separation of enantiomers.

The most widely used and effective methodology for the separation of enantiomers is liquid chromatography using a chiral stationary phase (CSP). Since the mid-1980's, the field of enantiomeric separations has progressed from something that was once considered difficult or impossible to do, to an essential and commonplace technique in pharmaceutical, bioanalytical, and synthetic organic laboratories (as well as in other areas). Cram and co-workers first introduced chiral crown ethers to the scientific community in the late 1970's [1,2]. Armstrong developed cyclodextrins and functionalized cyclodextrins as chiral recognition media in the early 1980's [3,4]. Concurrent with this work was the development of π-complex chiral selectors by Pirkle and co-workers [5,6] and two protein based chiral selectors by Swedish chemists [7,8]. Cellulosic and amylosic phases were introduced by Okamoto in 1984 [9]. Armstrong introduced macrocyclic antibiotics (esp. the glycopeptides) as chiral selectors in 1994 [10,11]. Finally, in 2009 Armstrong and co-workers discovered cyclofructan based chiral selectors [12].

As the quantity and importance of chiral drugs and biologically active compounds increases, there is a growing need to further develop and discover novel chiral column technologies. As noted above, for much of three decades, the development and study of chromatographic enantiomeric separations have been dominated by investigations which focused on selectivity. It is not a surprise that selectivity enhancements have been the focus given that conventional separation techniques used for all other molecules are ineffective for enantiomers. Thus, the most impactful studies dealt with development and optimization of better chiral selectors. However, the focus on enhancing enantiomeric selectivity, though very important, has resulted in a dearth of other technological advancements for chiral LC columns.

The column efficiencies of a typical 5 μm fully porous particle (FPP) based CSP are on the order of 25,000–50,000 plates/m. In other areas (*i.e.,* in achiral separations) HPLC column developments have seen tremendous advances in the past 10–15 years and achiral column efficiencies have reached 250,000–350,000 plates/m. Higher column efficiencies ultimately result in much shorter analysis times, greater success rates in developing robust separation methods, and an enhanced ability to quantitate impurities in a substance. Clearly, improvements in chiral column technology have lagged behind while other forms of liquid chromatography have improved greatly. As such, the development of chiral separation methods has become a bottleneck in the overall production of many new chiral drugs (and other important chiral compounds) in their pure enantiomeric state. This rate-limiting step in high-throughput new drug screening is a time consuming and costly process.

For this reason, there has been a recent thrust towards the improvement of chiral screening technologies and techniques, as well as, the development of new high efficiency CSPs. In this manuscript, the new methods for enhanced throughput and greater efficiency chiral separations will be discussed. The date range for this review will cover only 21st century reports, with a focus on those research papers published after 2010 as this is the timeframe where the new push towards greatly improved enantiomeric separations has occurred. Although there are other separation techniques that have seen advances in fast chiral separations (e.g. see the subsecond electrophoretic chiral separation from Piehl et al. [13]), we attempted only to cover HPLC, UHPLC, and SFC separations.

2. High-throughput methodology

HPLC and related techniques such as SFC have long been used to obtain qualitative and quantitative information from synthesis experiments [14]. The advent of high-throughput experimentation with micro-reactors, automation of laboratory equipment, and catalyst screenings have enabled researchers to perform a plethora of reactions in a single day [15–20]. With high volumes of samples to be analyzed, typical HPLC and SFC analysis times of 15–20 min can throttle productivity. Therefore, it is imperative to shorten these analysis times and adapt to the increased rate of experimentation. Continuous monitoring of process for content with on-line or at-line chromatography is an important aspect of process analytical technology for quality control. Ultrafast separations have become increasingly important in these areas to enable real-time monitoring and shorten response time to a change in process [21]. Second dimension separations in 2D-LC also require a fast method to separate analytes to avoid the wrap-around effect. Efforts have been made to increase the throughput of analyses with use of short and high-efficiency columns, multi-column parallel screening, multiple injections in a single experiment run (MISER), and rapid SFC gradient screening methods [15,22–27].

2.1. Multi-column parallel screening

Method development on HPLC or SFC to screen for enantioselectivity is typically performed with automated switching of columns and takes significant time with the one column at a time approach. When the need to increase the throughput arises, the easiest solution is using multiple instruments to perform screening or analysis in parallel. Although simple, this approach is rather tedious as the samples need to be divided between instruments, multiple instruments need to be operated individually, and data needs to be consolidated for subsequent analysis. Need for better alternatives for parallel analysis stemming from increased throughput of experimentation has led to development of methods for multi-column parallel screening and analysis [15,22,25,28].

An overview of different approaches to achieve parallel HPLC analysis is provided in Fig. 1 [15]. Fig. 1(a) describes a set up with independent injection and independent flow. In this type of system, each channel can be operated as an independent HPLC with different column (or geometry), chromatography mode, mobile phase composition, flow rate, and gradient program. This type of system can be very useful in high-throughput parallel screening or analysis. A commercial Express-800 parallel microflow HPLC is available from Eksigent Technologies that provides 8 separate channels with independent dual pumps (total 16), injectors, and detectors. Although very versatile and flexible, this system is also very complex and expensive [15,22,25,28]. Fig. 2 illustrates a multi-column parallel HPLC analysis of samples resulting from a catalysis reaction on 8-channel Express-800 system. Parallel HPLC allows screening of various conditions quickly to have the results available the same day, as opposed to the next day. Proper arrangement of the chromatograms, as seen in Fig. 2, allows easy visualization to scan for potential "hits". In this case, #9 in channel 5 appears to be the best condition for the separation.

Fig. 1(b) describes a system that uses a shared pump with independent injectors. Although this set up is simplified compared to Fig. 1(a), shared flow dictates that each channel must use the same

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