Journal of Chromatography A, 1382 (2015) 98–116

Contents lists available at ScienceDirect

Journal of Chromatography A

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

Review

Microfluidics-to-mass spectrometry: A review of coupling methods and applications

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ARTICLE INFO

Article history:
Received 22 August 2014
Received in revised form 9 October 2014
Accepted 12 October 2014
Available online 23 October 2014

Keywords:
Proteomics
Metabolomics
Lab-on-a-chip
Integrated devices
Bioanalysis

ABSTRACT

Microfluidic devices offer great advantages in integrating sample processes, minimizing sample and reagent volumes, and increasing analysis speed, while mass spectrometry detection provides high information content, is sensitive, and can be used in quantitative analyses. The coupling of microfluidic devices to mass spectrometers is becoming more common with the strengths of both systems being combined to analyze precious and complex samples. This review summarizes select achievements published between 2010 and July 2014 in novel coupling between microfluidic devices and mass spectrometers. The review is subdivided by the types of ionization sources employed, and the different microfluidic systems used.

Contents

1. Introduction

Microfluidic devices have greatly affected the field of analytical chemistry since their introduction in the early 1990s. These devices, made using a variety of fabrication techniques and materials, offer numerous advantages over comparable bench-top instruments [1,2]. Miniaturization with the subsequent reduction in sample and reagent volumes is a key advantage. It is now feasible to use and manipulate volumes that are orders of magnitude lower than

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http://dx.doi.org/10.1016/j.chroma.2014.10.039
0021-9673/

what was possible a few decades ago. Another advantage specific to microfluidic devices include integration of multiple analytical processes onto a single platform with very little dilution, increasing the overall sensitivity of the assay [3,4]. The nature of the fabrication process also allows reliable production of parallel analysis domains for automated and high throughput assays, which reduces sample handling and errors associated with manual manipulations [5].

Despite these advantages, there are numerous pitfalls surrounding the use of microfluidic systems. One limitation is the difficulty in coupling these devices to conventional macro-scale systems, such as external pumps or detectors. Because of this difficulty, optical detection, most notably fluorescence detection, is often the detection method of choice due to its ease in obtaining information within the confines of micro-channels [6]. And while this detection method is extremely sensitive, it is non-universal requiring the use of fluorescent reporters. Electrochemistry is also a convenient means of detection in microfluidic systems due to the ability to miniaturize many of the components [7]. However, the same problems with specificity occur with electrochemical detection as encountered with optical detection, in addition to difficulties decoupling detection electronics with the high voltages used to drive fluid flow.

Mass spectrometry (MS) offers a near universal approach for detection than optical or electrochemical methods. However, MS detection from microfluidic systems has not been explored as much as these other methods. One reason for this lack of popularity may be due to the difficulty in coupling the analyses performed on microfluidic devices to the off-chip mass spectrometer. This entails sampling microliter to picoliter volumes from the device after chip-based analysis is performed. And while this coupling can be problematic, the information obtained from MS analysis is often worth many of the difficulties encountered.

The purpose of this review is to highlight several papers published between 2010 and July 2014 that describes novel coupling mechanisms or applications of microfluidic systems to MS detectors. We outlined this review into microfluidic systems coupled to electrospray ionization (ESI), matrix-assisted laser desorption ionization (MALDI), and other ionization methods. Within each of these categories, we subdivided into the main microfluidic systems employed, conventional or analog, droplet, and digital microfluidic systems. We wrote this review assuming the reader understands the fabrication methodologies of microfluidic devices, but point out unique aspects during the discussion of the individual papers. In the conclusion, we note a few intriguing possibilities for future coupling strategies. It should be noted that we did not intend to make this a comprehensive review of the literature, and point the reader to other reviews that provide additional viewpoints or time frames on this subject [8–12].

2. Microfluidics coupled to ESI-MS

Due to its ease in accepting low flow rates, ESI is compatible with microfluidic devices. As a result, it has been a widely exploited ionization method for on-line microfluidic-MS analysis. With the continued development of microfabrication technology, coupling of the main types of microfluidic systems (analog, digital, and droplet microfluidics) to MS via ESI has become more common, and a number of successful examples have been achieved.

2.1. Analog microfluidics ESI-MS

Analog, or conventional, channel-based microfluidics are often utilized due to their wide versatility in a number of analyses, such as sample preparation, preconcentration, micro-reactions, and separation. In this section, we describe the most common means of coupling analog microfluidic systems to ESI-MS followed by select applications using these systems.

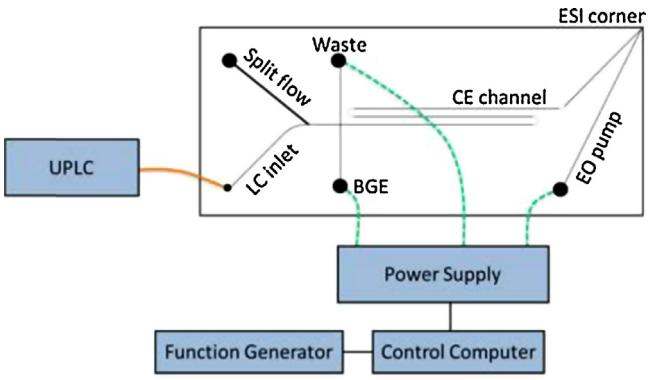

Fig. 1. Hybrid capillary LC microfluidic CE-ESI. A capillary LC system is connected to the microfluidic device as shown by the orange line. The electrical connections to control the microfluidic CE-ESI system are shown by the green lines. To compensate for flow rate differences between the LC and CE system, the majority of the LC eluent was split to waste via the split flow channel.
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2.1.1. Coupling to ESI-MS via integrated emitters

Several approaches have appeared in the literature for coupling emitters from a microfluidic device to interface with ESI-MS. These means of coupling can be classified into two main categories: spraying from integrated emitters and spraying via external emitters.

Integrated emitters are made directly within the device during fabrication producing connections with no, or very little, dead volume. A simple means to produce this type of emitter is to fabricate the channel of interest, such as a separation channel, so that it extends to the edge of the device. Application of the electrospray voltage is achieved through a secondary channel that intersects the separation channel near the edge of the device. In this way, it is also possible to introduce sheath flows containing the appropriate buffers or organic solvents to increase spray efficiency. Although the fabrication of this type of coupling strategy is straightforward, one drawback to this design is wetting of the microfluidic substrate by the separation eluent [13]. The low contact angle that the hydrophilic liquids have on the glass leads to sample spreading on the chip edge and generates a relatively large Taylor cone, which introduces dead volumes at the microchannel exit and may negatively influence the separation. Hydrophobic coatings on the hydrophilic channels have been tested but are not stable over time [14]. Moreover, even on hydrophobic substrates, the Taylor cone tends to form at the site of the most protruding microdefect since it experiences the highest local electric field strength [15]. This inability to accurately control the position of the spray will reduce the spray efficiency. To overcome these limitations, the channel of interest is directed toward a sharpened point on the device to limit the surface area that the eluent comes into contact with as it sprays from the device.

Over the past two decades, Ramsey's group has explored online coupling of microfluidic chips to MS [16]. In recent work, they have developed an integrated capillary liquid chromatography (LC)/capillary electrophoresis (CE)-ESI-MS system to study proteolytic digests [17]. To compensate for flow rate differences between the offline capillary LC system (~500 nL/min) and the microchip CE system (~100 nL/min), a split flow channel was employed after introducing the LC eluent into the chip as shown in Fig. 1. With the split channel having a low resistance to flow, the LC eluent delivered to the CE domain was reduced to a level that was compatible with electroosmotic flow (EOF). The glass microchip was coated with 3-(aminopropyl)triethoxysilane (APTES) to produce a