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Advances in and prospects of microchip liquid chromatography

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ABSTRACT

This study focuses on recent advances (from January 2013 through April 2015) in microfluidic liquid chromatography. Articles published during this period are organized by the type of stationary-phase support focusing on device fabrication, column preparation, and specific applications. In addition, a comprehensive table comparing chromatographic figures of merit for this study is provided in Appendix A as a reference for readers.

Contents

1. Introduction

In their study on column technology in 2012 [1], Gritti and Guiochon discussed future directions for small-diameter (10–300 μm) liquid chromatography (LC) columns used at high pressures and speeds. Because of these small diameters, a 50-mm-long column packed with 1-μm particles would have a small band variance (for an analyte with $k'=3$ at a reduced plate height of 3 μm) of 3 nL^2, which would be unsuitable for standard instrumentation with extra-column variances (due to injection, detection, and connecting tubes) on the order of 10,000 nL^2 [1]. Indeed, the need to reduce extra-column band broadening in LC microcolumns has been a key challenge to researchers in the field for >30 years [2]. In addition, for a column of this size packed with these smaller particles, optimum linear velocities would generate pressures up to 4000 bar. Higher-speed separations with such a column would require end-fittings that can handle pressures far exceeding this value. In order to resolve these issues, Gritti and Guiochon suggested the fabrication of a single device capable of withstanding pressures up to 10,000 bar with integrated injection and detection directly on the column [1]. While such an engineering feat is likely many years away, this review highlights recent work in microchip LC focused toward this ultimate goal, together with future developments and alternate trends to reduce cost and complexity. This study emphasizes advances since previous in-depth reviews [3–6], and focuses on the LC column and

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separation; further information on coupling such devices to mass spectroscopy (MS) has been described earlier [7–10].

Literature searches using Web of Science, SciFinder, PubMed, and Google Scholar revealed that >350 articles pertaining to microchip LC were published from January 2013 to April 2015. Majority of these articles focused on the use of commercial chip-LC systems by Agilent Technologies [11], Waters Corporation [12], and Eksigent Technologies (part of SCIEX) [13] and emphasized specific applications. Rather than discuss the use of these widely available systems, technologically driven investigations are highlighted that might guide future developments in the field.

2. Discussion

The first experimental demonstration of LC on a chip was reported 20 years ago [14]. The system consisted of a microfabricated silicon glass fluidic network that incorporated a split-injection tee, a channel packed with 5-µm reversed-phase particles adjacent to a series of smaller channels that could act as a particle-retaining frit, and an optical detection flow cell. The chip was placed in a clamping device that enabled connection of fused silica capillary to and from the chip for connection to an external pump and injector [14]. Although the efficiency of this first chip-LC column was poor, its early design spawned much research into new ways of preparing columns, integrating components, and applications [15–17]. Of particular interest have been the different column types incorporated into chips as particles, monoliths, and pillar arrays, which have all been used as stationary-phase supports. In principle, open-tubular LC columns on chip are also possible; however, few articles have been published on this format in the past 2 years. The advantages and drawbacks of the different support systems are summarized in Table 1 [3]. A summary of the column dimensions and performance metrics of several examples of the different column types is given in Appendix A.

2.1. Particle-packed columns

2.1.1. Particle-retaining frits

As described in Table 1, one of the drawbacks of packed beds on microchips is the need for retaining frits to keep the particles in place [3]. Although several fritting techniques have been developed for capillary LC columns [18], most chip-LC frits have relied on the blockage of particles through channel constrictions or weirs (relying on the keystone effect) [3]. One drawback of these types of frits is that usually only the outlet end of the column can have a frit on it, which limits flow to a single direction and can lead to particle loss at the inlet. Recently, a two-weir column channel has been described that eliminates both particle loss and the need for a connecting channel between the sample injector and the head of the column [19]. A side-packing channel is used to enable the filling of the channel. This packing channel then is completely closed to flow using an ultraviolet (UV)-polymerized monolith solution, eliminating any extra-column broadening that might occur due to this layout [19]. This polymer technique was later modified such that the actual monolith itself could be used as a frit [20]. With these porous polymeric monolith (PPM) frits (Fig. 1), beds can be packed

Table 1
Advantages and disadvantages of three different stationary-phase supports. Used with permission from Elsevier from ref. [3]

Support Type	Advantages	Disadvantages
Particles	• Many stationary-phase selectivities available • High batch-to-batch reproducibility • High loadability	• Packing quality dependent on packing skills • Retaining frit required • Higher back pressures generated
Monoliths	• Lower back pressure than particle-packed beds • No packing or frits (mostly) required • Different base chemistries available	• Inherent variations in synthetic approach (lower batch-to-batch reproducibility) • Synthesis procedure can depend on chip substrate
Pillar Arrays	• Ordered structure can result in higher efficiency than random-packed bed • Can be fabricated by nanoprint lithography (for mass production)	• Limited loadability • Hard to make porous (and doing so can affect performance) • Sophisticated fabrication techniques required

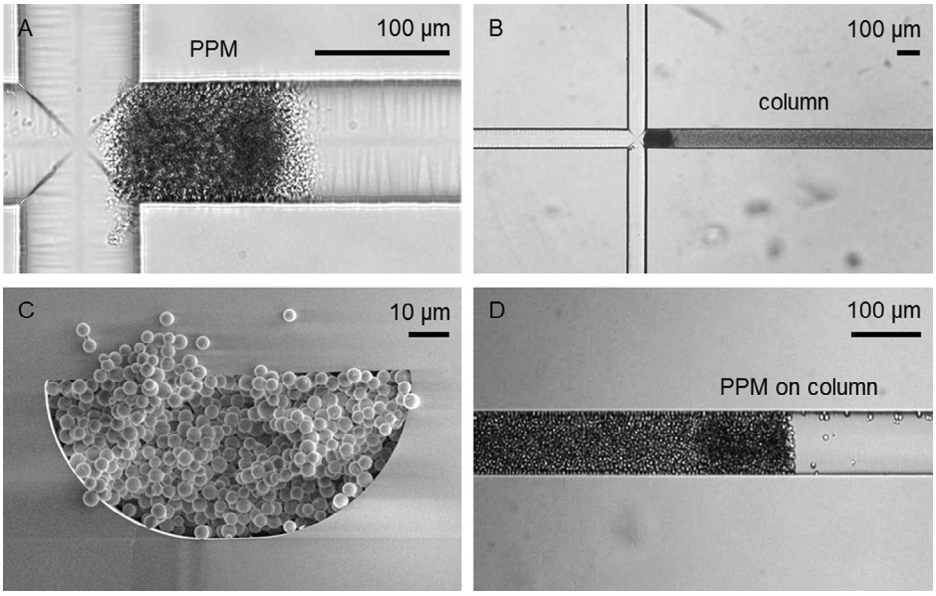

Fig. 1. Fabrication of a packed bed using porous polymeric monolithic (PPM) frits. First, the inlet frit is formed adjacent to an injection cross (A), and a column bed is packed in reverse against this frit (B, with column cross section shown in C). Then, an outlet frit is polymerized at a distance equal to the desired length of the column, and the remaining particles are flushed out of the outlet (D). Used with permission from Elsevier from ref. [20].