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Review

Particle-based liquid chromatographic separations in microfluidic devices - A review

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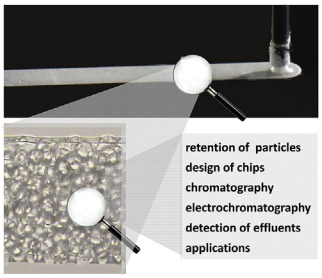
HIGHLIGHTS

- The LC chips received outstanding attention due to their special advantages.
- This work reviewed the particle based liquid chromatographic chips.
- Incorporating the micro- or nano-particles into microchips is still a challenge.
- The robustness of LC chip's operation is highly requested to improve.
- The LC chip MS systems are expected to widely spread in the future.

GRAPHICAL ABSTRACT



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ABSTRACT

The research and applications of liquid chromatographic (LC) chips receive more and more attention due to the numerous advantages over the traditional and larger analytical systems, e.g. requirement for small sample and reagent volumes, fast and inexpensive analysis, dead-volume free connections and the ability to multiplex measurements. Since LC is one of the most powerful separation techniques, its miniaturization seems an obvious target of lab-on-a-chip developments. However, the common procedures used in the preparation of chromatographic columns are not well applicable at the microscopic level. Additionally, implementing sample injection of (sub)nanoliter volumes (with sensitive detection) is still a challenge.

This review deals with microchips incorporating particle-based stationary phases and focuses on the lab-made and commercialized chromatographic separations discussing the particle retention methods, the designs/constructions of LC chips, the separation performances and possible applications. A survey about microfluidic chips - capable of efficient separations and high-throughput sample pretreatment - hyphenated with electrospray mass spectrometric devices to achieve sensitive detection has also been made. The merits and limitations of different commercial LC chips were compared with other published approaches, as well.

Contents

1. Introduction 00
2. Particle retention in microfluidic channels 00

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2.1. Fritless methods 00
2.2. Methods using frits or other frit-like physical barriers 00
3. Designs of microchips 00
3.1. Material 00
3.2. Sample injection and fluid control 00
3.3. Separation modes 00
3.4. Detection 00
3.5. Commercial LC chip systems 00
4. Separation performances 00
5. Applications 00
6. Conclusions, future outlook 00
Acknowledgements 00
References 00

Abbreviations

BSA	bovine serum albumin
CARS	Coherent anti-Stokes Raman scattering
CE	capillary electrophoresis
CEC	capillary electrochromatography
COC	cyclic olefin copolymer
CZE	capillary zone electrophoresis
EC	electrochromatography
EOF	electroosmotic flow
ESI	electrospray ionization
FIA	flow injection analysis
GIG	glycoprotein immobilization for glycan extraction
HILIC	hydrophilic interaction liquid chromatography
ICP	inductively coupled plasma
IMAC	immobilized metal affinity column
IMER	immobilized enzyme reactor
LC	liquid chromatography
LED	light-emitting diode
LIF	laser-induced fluorescence
LOD	limit of detection
LOQ	limit of quantitation
MALDI	matrix-assisted laser desorption/ionization
μCP	microcontact printing technology
μTAS	micro total analysis system
MCEC	microchip electrochromatography
MS	mass spectrometry
MSL	multilayer soft lithography
NDV	Newcastle disease virus
PDMS	polydimethylsiloxane
PMMA	polymethylmethacrylate
PNGase F	peptide-N-Glycosidase F
SPE	solid phase extraction
SCX	strong cation exchange

1. Introduction

In the last few decades one of the most important efforts in analytical chemistry is about the developments of miniaturized systems, because they provide many advantages over conventional analytical methods including requirements for small sample and reagent volumes, portability, fast and cheap way of analysis or the ability to multiplex measurements. Since liquid chromatography (LC) is the most extensively studied and applied analytical method, there is particularly high demand for its miniaturization. In LC systems miniaturized into the size of a few square centimeters (LC chip), different types of stationary phases have been constructed. As the simplest case, chromatographic separations can be performed in (coated) open channels often conducted in a complex design to reach high surface-to-volume ratio [1]. The in situ generation of monoliths in microchannels is a relatively simple approach, as well [2]. However, several disadvantages of monolithic columns, e.g. possible wall effects or poor reproducibility/characterization of (commercial) columns are well-known. A much better sample loading capacity and higher separation efficiency can be achieved on particle-based stationary phases. Since a very large variety of porous chromatographic particles are available on the market, the developments, application fields and knowledge on conventional LC can be utilized and converted to microchips.

In spite of the obvious demands and expectations, only relatively few LC chip developments have been reported compared to microfluidic electrophoresis devices. It is interesting that although the first reported microfluidic chip was an open-tubular LC chip [1], mainly electrophoretic chips have been developed in the following years due to their simpler construction and operation. The main obstacle in the miniaturization of conventional particle-based LC systems was the difficulty to reproducibly prepare compact chromatographic micropackings in microscopic channel systems, which can tolerate high pressure during usage. Other challenges - like the reproducible formation of nanoliter sample plugs and their sensitive detection - are easier to handle.

Although the development of particle-based chips would be expected as the favored trend, relatively few publications can be found compared to open-tubular or monolithic LC chips due to the difficulty in preparing frits or appropriate packings. A few companies solved the problem of frits quite well (e.g. Agilent Technologies created frits in three laminated polyimide layers chip using laser ablation [3]) utilizing high-tech micromachining procedures, but typical research laboratories do not possess such infrastructure and thus are not able to create LC chips capable of high performance separations. Instead, research laboratories can either cooperate with such companies/institutions, apply a commercialized LC chip system or their research may target a special issue of the LC chip system (but mainly not high-performance separation that can be achieved by modern HPLC/UPLC instruments). Unfortunately,

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