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Review

Solid supports for extraction and preconcentration of proteins and peptides in microfluidic devices: A review

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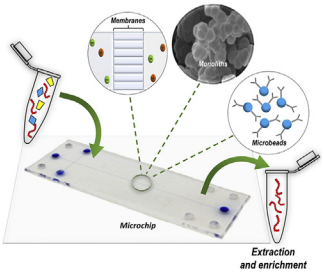
HIGHLIGHTS

- Miniaturization offers unique opportunities for extraction and preconcentration.
- Solid supports include microbeads, monoliths and membranes.
- High performances are achieved *via* the synergy of microfluidics and solid supports.
- Integrated microsystems enable analysis of complex samples.

GRAPHICAL ABSTRACT



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ABSTRACT

Determination of proteins and peptides is among the main challenges of today's bioanalytical chemistry. The application of microchip technology in this field is an exhaustively developed concept that aims to create integrated and fully automated analytical devices able to quantify or detect one or several proteins from a complex matrix. Selective extraction and preconcentration of targeted proteins and peptides especially from biological fluids is of the highest importance for a successful realization of these microsystems. Incorporation of solid structures or supports is a convenient solution employed to face these demands. This review presents a critical view on the latest achievements in sample processing techniques for protein determination using solid supports in microfluidics. The study covers the period from 2006 to 2015 and focuses mainly on the strategies based on microbeads, monolithic materials and membranes. Less common approaches are also briefly discussed. The reviewed literature suggests future trends which are discussed in the concluding remarks.

Abbreviations: Aβ, β amyloid; BSA, bovine serum albumin; CEA, carcinoembryonic antigen; CP, concentration polarization; DMF, digital microfluidics; EDL, electric double layer; ELISA, enzyme-linked immunosorbent assay; EOF, electroosmotic flow; GFP, green fluorescent protein; HAS, human serum albumins; HSP, heat shock proteins; IL, interleukin; IMAC, immobilized metal-affinity chromatography; LC, liquid chromatography; MALDI, matrix-assisted laser desorption ionization; MMP, matrix metalloproteases; OVA, ovalbumin; PE, phycoerythrine; POC, point-of-care; SPE, solid phase extraction; TSH, thyroid-stimulating hormone; μCE, microchip electrophoresis; μTAS, micrototal analysis system; MPTMOS-3, trimethoxysilylpropylmethacrylate; GPTMOS, glycidyloxypropyltrimethoxysilane; EDMA, Ethylene dimethacrylate; BMA, butyl methacrylate; EGDMA, Ethylene glycol dimethacrylate; GMA, Glycidyl methacrylate; TMPTMA, Trimethylolpropane trimethacrylate; BA, butyl acrylate; BDA, butyl diacrylate; LA, lauryl acrylate.

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Contents

1. Introduction

Microchip technology emerged in the early 1990s and was rapidly adopted in various fields of life science [1–3]. Especially the concept of micro-total analysis systems attracted a lot of attention [4] and soon after, the first automated microdevices were reported [1,2]. In practice, development of a so called lab-on-a-chip platform faces many difficulties including sampling, sample processing, mixing and detection, just to mention but a few [5]. The sample preparation step is usually considered as a bottle neck of the whole analytical procedure and, as such, deserves special attention.

Performance of extraction/enrichment in chip format is challenging due to the microscale of the whole process. Its successful implementation requires proper design of the system of microchannels and chambers. The layout complexity is usually less demanding in the case of solid supports in comparison to liquid-based processes (like liquid-liquid extraction) as the whole procedure can be conducted in a single channel [6]. This also raises the major issue of liquid mixing in microdevices and makes the former solution more preferable than the latter one. Moreover, a variety of available chemical modifications and great preconcentration potential additionally supports selection of solid supports. Only electrokinetic techniques like field amplified stacking methods or sweeping feature higher enrichment efficiency in comparison to solid phase extraction (SPE). However, they are generally devoid of selectivity and are less efficient for highly saline sample analysis like biological fluids. Preconcentration strategies based either on electrokinetic process or on solid supports and adapted to microfluidics were thoroughly reviewed by Lin et al. and Giordano et al. and the reader is strongly encouraged to get acquainted with these comprehensive papers [7,8].

The main difficulty in employing solid supports lies in their integration in to the microsystem. A number of approaches have been published to date for on-chip extraction and preconcentration including packed [9] and monolithic [10] beds, membranes [11,12], micropillars [13] or microchannel surface modifications [14]. However, these are only the most common solutions. Adoption of a certain support brings a number of advantages and disadvantages which makes the decision on the appropriate option difficult. Further considerations include the chemistry of the support which depends on the characteristics of the targeted compounds.

Proteins are clinically relevant molecules especially for diagnostic purposes. Extraction of these substances is a challenging task due to their complex structure and non-uniform properties. The issue is even more complicated considering the fact that most of the proteins identified as validated biomarkers are at extremely low abundance [15]. Trace level of proteins in analyzed samples and microscale of in-chip processes make the enrichment of targets as important as their selective isolation from the sample matrix. Numerous solutions have been proposed in the literature for the efficient extraction and preconcentration of proteins. Among them, directly transferred macroscopic techniques were implemented in a miniaturized form and novel approaches taking full advantage of the microscale were presented [16–18]. The early steps in the field were summarized by Freire and Wheeler in 2006 [19]. Likewise, Peterson published a comprehensive review on solid supports for on-chip applications and just after De Jong and coworkers reviewed the use of membrane techniques in microfluidics [20,21]. However, the latest published reviews dealing with the principles of extraction and preconcentration in microfluidic [22,23] lacked more detailed discussion on the topic of peptides and proteins. Other articles solely include selected topics on monoliths [24] or membranes [16,17]. Since Freire and Wheeler's publication [19], no comprehensive paper summarizing the latest achievements in extraction and preconcentration of proteins and peptides in chips has been provided.

The present review covers the application of the solid supports for extraction and preconcentration of peptides and proteins in microfluidics over the period of the last 10 years. It entails standard peptides/proteins as well as toxins and biomarkers in different media from simple solution to complex biological fluids. The well-established strategies based on microbeads, monoliths and