



Review

Recent advances in microfluidic sample preparation and separation techniques for molecular biomarker analysis: A critical review



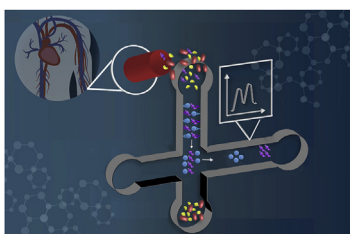
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HIGHLIGHTS

- We critically review recent advances in using microfluidic devices for biomarker sample preparation and separation.
- We discuss improvements in on-chip sample preparation, including affinity extraction, preconcentration and labeling.
- We highlight developments in molecular biomarker separations.
- We provide a critical evaluation of papers, detailing promising directions for additional work.
- We discuss possible future trends that will help to increase the impact of microfluidics in improving human health.

GRAPHICAL ABSTRACT



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ABSTRACT

Microfluidics is a vibrant and expanding field that has the potential for solving many analytical challenges. Microfluidics show promise to provide rapid, inexpensive, efficient, and portable diagnostic solutions that can be used in resource-limited settings. Researchers have recently reported various microfluidic platforms for biomarker analysis applications. Sample preparation processes like purification, preconcentration and labeling have been characterized on-chip. Additionally, improvements in microfluidic separation techniques have been reported for molecular biomarkers. This review critically evaluates microfluidic sample preparation platforms and separation methods for biomarker analysis reported in the last two years. Key advances in device operation and ability to process different sample matrices in a variety of device materials are highlighted. Finally, current needs and potential future directions for microfluidic device development to realize its full diagnostic potential are discussed.

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1. Introduction

Disease diagnostics are important for improving human health, and the effective treatment of many life-threatening conditions is dependent upon the accuracy and speed of the diagnosis, which can result in improved human life expectancy. Technologies currently used in healthcare diagnostics often require expensive instrumentation or a modern testing laboratory, neither of which are feasible in many developing nations or in remote locations. Hence, low-cost, rapid, portable, and easy to use tools are desirable to advance clinical diagnostics, especially in developing countries or remote areas that lack appropriate infrastructure.

Analyses of biomarkers, biomolecular indicators of medical conditions, hold excellent potential for the clinical diagnosis of various diseases. These biomarkers are frequently found in complex biological matrices or bodily fluids, which almost always require sample preparation prior to analysis. Sample preparation steps often need large volumes (>mL) and experienced personnel, which further increase the analysis time and cost. Thus, fast and effective sample preparation techniques are necessary to facilitate early diagnosis.

Microfluidic systems offering advantages like low cost per device, rapid analysis, and small sample requirements [1] have potential to transform diagnostics, especially in developing countries or remote locations due to amenability to point-of-care testing. Biomarker analysis has been one of the most actively pursued applications in miniaturization of chemical analyzers. A number of microfluidic systems have been reported recently that can perform sample preparation steps like purification, preconcentration and labeling on a chip prior to quantitation [1–3]. Separation techniques have also advanced for the analysis of molecular biomarkers in a microfluidic setup.

This manuscript critically reviews microfluidic techniques reported for biomarker sample preparation and separation over the last two years. Developments in microfluidics for biomarker analysis prior to 2015 have been reviewed previously [4,5]. Herein, we specifically focus on microfluidic sample preparation methods, such as biomarker purification from biological matrices and preconcentration of trace components, and approaches that are used for biomarker separation. Furthermore, novel aspects of device design and analysis methods are highlighted.

2. On-chip sample preparation methods

Microfluidics can be used to miniaturize and integrate sample preparation processes on a microchip platform. Typically, building these systems requires innovations in device design and manufacturing; fluid transport, automation and control; preparation of samples before analysis; separation; multiplexing; and detection [6]. Often sample specimens are limited in volume, contain matrix-related interferences, require multiplex analysis and have low target analyte concentrations [7]; therefore, sample

preparation is a key part of analysis. Commonly used sample preparation processes include analyte purification, enrichment and labeling. In this section we focus on select techniques for microfluidic sample preparation.

2.1. Molecular affinity extraction

On-chip sample preparation can be used to selectively extract, preconcentrate and label target analytes in an automated fashion. The ability to extract trace amounts of desired analytes from a complex sample matrix such as blood significantly simplifies the analysis [8]. Such on-chip sample preparation could replace laborious benchtop processes, and thus decrease analysis time and potentially allow point-of-care usage. Affinity approaches using antibodies or aptamers on a solid support can purify target species in blood or other complex samples from undesired matrix components that complicate analysis. A summary of key information related to molecular affinity extraction work discussed in this section is given in Table 1.

2.1.1. Antibody-based extraction

An antibody (Ab) offers high selectivity and specificity towards its target antigen, and can be used in microfluidic systems for the selective capture of desired molecules [9,10]. Antibodies can be placed in a microfluidic setup by device surface modification [11,12] or through a solid support like porous polymer monoliths [13], beads [14,15] or nanoparticles [16,17] introduced into microchannels.

An immunosensor was developed on a PDMS treated glass microfluidic device using Ab-conjugated polyvinyl alcohol covered zinc oxide nanoparticles for the extraction of epithelial cell adhesion molecule (EpCAM), a biomarker for epithelial cancers [18]. Whole blood was centrifuged and lysed off-chip to prepare the supernatant that was introduced into the microfluidic devices. Bound EpCAM interacted with anti-EpCAM conjugated to horseradish peroxidase, which catalyzed the oxidation of non-fluorescent 10-acetyl-3,7-dihydroxyphenoxazine to fluorescent resorufin, as shown in Fig. 1a. Extraction results from blood samples obtained from cancer patients and healthy volunteers were compared to a commercially available test, and a linear correlation was obtained from 2 to 2000 pg mL⁻¹ EpCAM with a detection limit of 1.3 pg mL⁻¹. Future work in correlation of measured EpCAM levels with cancer incidence with minimum off-chip sample preparation would be impactful.

In a different study a paper microfluidic device was reported that utilized an antibody-based sandwich assay for detection of tumor necrosis factor alpha (TNF α), an inflammation biomarker [19]. Carbon electrodes were printed on the paper device and anti-TNF α immobilization through both covalent binding and physical adsorption was tested for immuno-capture and electrochemical detection, as shown in Fig. 1b. The limit of detection for TNF α was 4 ng mL⁻¹, and diluted human serum samples spiked with TNF α

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