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Review

A review on recent developments for biomolecule separation at analytical scale using microfluidic devices

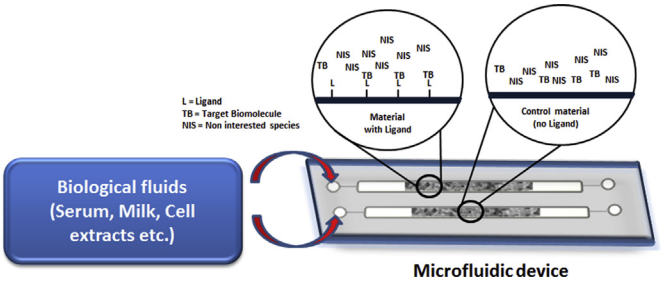
Kishore K.R. Tetala*, M.A. Vijayalakshmi

Advanced Centre for Bioseparation Technology (CBST), VIT University, Vellore, 632014, Tamil Nadu, India

HIGHLIGHTS

- Stationary phase material incorporation within microfluidic chips.
- Surface functionalization and ligand immobilization strategies.
- μfluidic chips have significant biomolecule adsorption than conventional devices.
- Identification of low abundant proteins in complex samples using μfluidic devices.

GRAPHICAL ABSTRACT



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ABSTRACT

Microfluidic devices with their inherent advantages like the ability to handle 10^{-9} to 10^{-18} L volume, multiplexing of microchannels, rapid analysis and on-chip detection are proving to be efficient systems in various fields of life sciences. This review highlights articles published since 2010 that reports the use of microfluidic devices to separate biomolecules (DNA, RNA and proteins) using chromatography principles (size, charge, hydrophobicity and affinity) along with microchip capillary electrophoresis, isotachophoresis etc. A detailed overview of stationary phase materials and the approaches to incorporate them within the microchannels of microchips is provided as well as a brief overview of chemical methods to immobilize ligand(s). Furthermore, we review research articles that deal with microfluidic devices as analytical tools for biomolecule (DNA, RNA and protein) separation.

Abbreviations: AAM, acrylamide; AC, affinity chromatography; AFP, alpha fetoprotein; AMPS, 2-acrylamido-2-methylpropanesulfonate; APTES, (3-aminopropyl)triethoxysilane; APDIPES, (3-aminopropyl)di-isopropylethoxysilane); BMA, butyl methacrylate; BSA, bovine serum albumin; CE, capillary electrophoresis; CEA, carcinoembryonic antigen; μCGE, micro-capillary gel electrophoresis; CIEF, capillary isoelectric focusing; CIM, convective interactive media; CMDCS, 10-(carbomethoxy)decyldimethylchlorosilane; COC, cyclic olefin copolymer; COP, cyclic olefin polymer; Con A, concanavalin A; cTnI, cardiac troponin I; cTnT, cardiac troponin T; CVD, chemical vapour deposition; DATD, (+)-N,N′-diallyltartardiamide; DEGDME, diethylene glycol dimethyl ether; EDA, ethylene diacrylate; EDMA, ethylene dimethacrylate; EOP, electroosmotic pumping; ESI-MS, electrospray ionization-mass spectrometry; FITC, fluorescein isothiocyanate; GFP, green fluorescent protein; GMA, glycidyl methacrylate; GOx, Glucose oxidase; HEMA, 2-hydroxyethyl methacrylate; HIC, hydrophobic interaction chromatography; HSP90, heat shock protein 90; IDA, iminodiacetic acid; IEX, ion exchange chromatography; IgE, immunoglobulin E; ITP, isotachophoresis; LMT, low-melting temperature; MBAAm, N,N′-methylene bisacrylamide; MCE, microchip electrophoresis; μMEEKC, microemulsion electro kinetic chromatography; META, (2-(methacryloyloxy)ethyl) trimethylammonium chloride; Myo, myoglobin; MMA, methyl methacrylate; NW, nanowire; NHS, N-hydroxysuccinimide; NVP, N-vinyl pyrrolidone; PCB, printed circuit board; PCR, polymerase chain reaction; PDA, piperazine diacrylamide; PDMS, polydimethylsiloxane; PE, polyethylene; PECVD, plasma enhanced chemical vapour deposition; PEG, polyethylene glycol; PMMA, poly(methylmethacrylate); PNA, *arachis hypogaea*; RPC, reverse phase chromatography; SDS, sodium dodecyl sulphate; SEC, size exclusion chromatography; TAMRA, 5-carboxytetramethylrhodamine; TSPM, 3-(trimethoxysilyl)propyl methacrylate; VLS, vapour–liquid–solid.

* Corresponding author. Advanced Centre for Bioseparation Technology (CBST), 6th Floor, Technology Tower, VIT University, Vellore, 632014, Tamil Nadu, India.
E-mail address: kishore.tetala@gmail.com (K.K.R. Tetala).

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Contents

1. Introduction

Separation and accurate identification of highly valuable biomolecules (nucleic acids, proteins, polysaccharides etc.) from complex biological fluids (serum, milk, cell extracts etc.) require utmost importance [1,2]. Limited sample volumes and pathological condition of specimens increase the complexity for selective separation and identification of target analyte(s) that are present at micro- and nano-levels; for instance, a potential biomarker for proteomics, molecular diagnostics etc. Chromatographic methods efficiently separate biomolecules in pure form after initial sample pre-treatment but require large sample volumes and are relatively time-consuming. Capillary electrophoresis (CE) require smaller sample volumes and relatively fast, but can separate biomolecules only on the basis of charge-to-size. Microfluidic devices started to receive attention from the scientific community as an alternative to overcome the shortcomings of conventional devices [3–6]. A microfluidic device can be visualized as a planar miniature device that has a patterned network of multiplexed channels of ~5–500 μm diameter to handle liquids as low as 10^{-15} to 10^{-18} L [3,7]. Fig 1 depicts an integrated microfluidic device comprised of a multiplexed microchannel (for on-chip cell lysis) conjoined with a crown shape pattern channel (for RNA extraction) [8]. Readers are referred to reviews [3–6,9–15] and books [16–19] that highlight "(historical) overview" and fabrication technologies of microfluidic devices, their potential applications and achievements.

In 2008, Wu et al. [20] reviewed developments of microscale chromatography for biomolecule separation. Later in 2010, Vazquez and Paull [21] reviewed microfluidic systems (micro valves, electrospray emitters, micro mixers, and micro-reactors) for biomolecule separation with an emphasis on polymer material incorporated microchips. The focus of the current review is to provide an update on developments since 2010. In particular, we discuss the separation of biomolecules with respect to various chromatography techniques like Size Exclusion Chromatography (SEC), Ion Exchange Chromatography (IEX), Hydrophobic Interaction Chromatography (HIC), and Affinity Chromatography (AC). Besides these, Microchip capillary electrophoresis (MCE) based biomolecule separations [11,22–24], isotachophoresis (ITP) etc. are also included. Also reviewed here are research articles published in 2009 that fell out of scope of a previous review [21].

Development of a microfluidic device for biomolecule separation requires involvement and knowledge of chemistry and other branches of life sciences. For example, knowledge in chemistry helps to synthesize a variety of stationary phase materials and their modification for ligand attachment or surface functionalization to prevent non-specific adsorption of biomolecules on the microfluidic surface. In Section 2 and 3, we provide insights into stationary phase materials, their incorporation within the microchannels and chemical methods to modify the microchannels

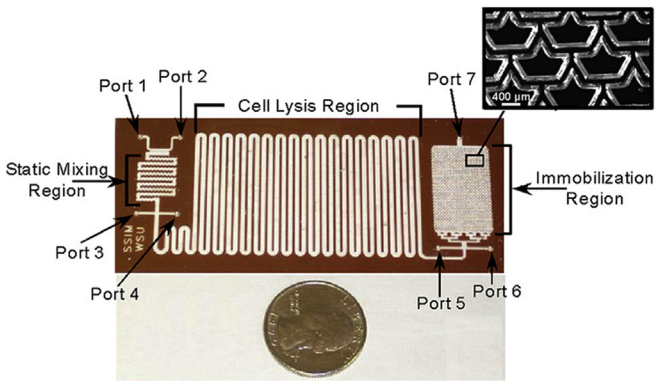

Fig. 1. An integrated microfluidic device for on-chip cell lysis and affinity extraction of RNA (reprinted with permission from Ref. [8]).