

Microfluidic paper-based analytical devices (μ PADs) for fast and ultrasensitive sensing of biomarkers and monitoring of diseases

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Summary

Through the development of analytical techniques, microscaled devices have displayed attractive advantages, including ultrasensitive detection and analysis, cost-effectiveness, portability, process integrity, multi-process functionality, and in-situ analysis. In the last decade, a new generation of analytical devices has emerged based on the cellulose materials – so-called microfluidic paper-based analytical devices (μ PADs) – a field that will change the face of the diagnosis of different diseases and sensing of a wide range of biological/chemical/biochemical phenomena. The main aim of the current editorial is to highlight the importance of the μ PADs in the research and development of diagnostic devices and pharmaceuticals.

Author's Biosketch

Abdollah Abdollahi-Aghdam (M.Sc. in Chemistry, 2014, University of Tabriz, Iran) is Ph.D. student at the University of Tabriz and works on the development of microfluidics devices.



Professor Mir Reza Majidi has a Ph.D. degree in conducting polymer (1996, University of Wollongong, Australia). He is now working as a full professor of chemistry at the University of Tabriz. His research has mainly been focused on the analytical chemistry. He has published over 100 articles in the field of analytical chemistry.



Professor Yadollah Omid has a Ph.D. degree in pharmaceutical Sciences (2003, Cardiff University, UK) and completed a postdoctoral program (2004) at Cardiff University. He is the founder of the Research Center for Pharmaceutical Nanotechnology (RCPN), the School of Advanced Biomedical Sciences at Tabriz University of Medical Sciences (TUOMS), the international peer-review journal "BioImpacts", and the National Institute of Medical Sciences. Prof. Omid's researches in advanced targeted diagnosis and therapy of diseases have resulted in over 180 published papers in international journals, 18 book chapters, and a few patents. During 20 years of experiences in different institutes (UK; Iran; and USA), his scientific life has been endowed with pharmaceutical sciences.



Paper has been used over the centuries for various experimental purposes such as litmus paper as pH indicator, while the first microfluidic paper-based analytical device (μ PAD) was introduced by Whitesides and colleagues in 2007.¹ The field of μ PADs has continued to develop at an exponential rate with notable impacts on the academic and industrial communities. These devices use cellulose as substrate to serve as paper-based analytical devices (PADs) for the point-of-care diagnosis, biosensing, environmental monitoring, biomedical and pharmaceutical analysis, clinical diagnosis, and forensic investigations.² Furthermore, paper has played an important role in chemical/biochemical analysis, including home pregnancy tests,³ paper chromatography,⁴ paper-based colorimetry, paper-based filtration and purification, pH test, etc. The popularity of PADs is based on several

advantages, including (i) very low-cost, (ii) power-free due to cellulose fiber networks,^{5,6} (iii) compatibility with small volume of samples, (iv) the ability to store reagents, (v) easy operation and construction, (vi) portability and disposability. Combination of the microfabrication techniques with the paper has resulted in the generation of *de novo* cost-effective analytical devices with robust easy and fast applications in different fields of sciences and technologies. Thus, some key insights of various types of papers are discussed, which are used as the substrate, methods for the construction of detection systems, and μ PADs for the detection and sensing of biomarkers.

The selection of a paper is largely dependent on the application and construction method. In the last years, Whatman® grade 1 filter, which is one of the standard grade filters, has widely been used in the construction of



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sensors and microfluidics, in large part because of their suitable flow rate, porosity, and particle retention.⁷⁻⁹ Some researchers have also used Whatman® grade 4 filters,¹⁰ Whatman® chromatography paper 1,¹¹ polyester-cellulose blended-paper,¹² and glass microfiber filters.¹³

There are various construction methods for the development of μ PADs. The first reported method has been based on the photolithography that provides a high-resolution structure between the hydrophilic and hydrophobic areas.¹ The wax screen-printing method is a low-cost and simple approach for the construction of the hydrophobic barriers.¹⁴⁻¹⁶ Polymeric organosilicon compounds have also been used for devising the μ PADs. In fact, polydimethylsiloxane (PDMS) plotting is deemed to be an excellent approach for the construction of μ PADs.¹⁷ In this method, a computer-controlled plotter is routinely used for plotting of the PDMS on the paper for the flow delivery in the microfluidics chips. Further, the development of bio-microelectromechanical systems (bio-MEMS) is extensively dependent on the soft lithography for imprinting of the microfluidic channels in both organic and inorganic settings. This technique offers several advantages, including (i) the lower cost than that of the traditional photolithography in terms of large-scale production, (ii) better pattern-transferring methods compared to the traditional lithography techniques and (iii) unnecessary of having a photo-reactive surface devising micro-/nano-design. Some other techniques have also been reported, including inkjet etching/printing,⁵ plasma etching,¹⁰ flexographic printing,¹⁸ and cutting¹⁹ as well as electron-beam lithography (EBL). Of these, EBL is believed to be one of the tools of choice for the imprinting micro- and/or nano-designs on the surface of a wide variety of materials, in large part due to its capability of imprinting the nano-sized structures on the tiny surface (up to mm²) with great details.

So far, we have developed and applied a number of different biosensors for the monitoring and sensing of various inorganic/organic materials using differently

advanced nanobiomaterials.²⁰⁻²⁶ The colorimetric detection is a cost-effective simplest method for the detection of various biological entities.²⁷⁻²⁹ This latter approach is largely dependent on the implementation of μ PADs. As a matter of fact, the integration of μ PADs with the electrochemical detection approaches were shown to provide a very useful, portable, accurate and robust detection systems – applicable for the detection in various types of settings.^{30,31} Other detection techniques like chemiluminescence,^{7,32} and fluorescence³³ can also be implemented using μ PAD technologies. The μ PADs are used in various fields, including environmental monitoring they of contaminations,³⁴ food safety,³⁵ health diagnostics,^{36,37} biodefense (micro-organisms sensing),^{38,39} and drug discovery³¹ as well as a biomarker and single cell detections. Fig. 1 represents a schematic illustration of the μ PAD technology.

The emergence of μ PADs is envisioned to overcome many barriers and even eliminate the traditional detection systems. In addition to the environmental monitoring (e.g., contaminations of water, soil and air),⁴⁰ the μ PADs have been utilized for the sensing of toxic agents in the biological samples as well as drug abuse.⁴¹ Although the μ PADs have originally been developed for the point-of-care diagnostic applications in developing countries, they are going to change the direction of clinical diagnosis of various types of diseases mechanistically, in large part because of being rapid, cost-effective, portable and reliable devices. Various biological molecules like DNA,⁴² proteins,⁴³ and cancer cells⁴⁴ have been detected by these devices. Their impacts on the detection of pathogenic microorganisms such as viruses and bacteria make them robust monitoring tools in the field of biodefense. For instance, Li et al developed a new paper-based device for the detection of avian influenza virus (AIV). Given that the detection of pesticide and residues of fertilizers in foods can improve the global health, their successful applications in tracking residuals have also been reported.³⁵ We envision that the μ PADs are in early development stage and are going to

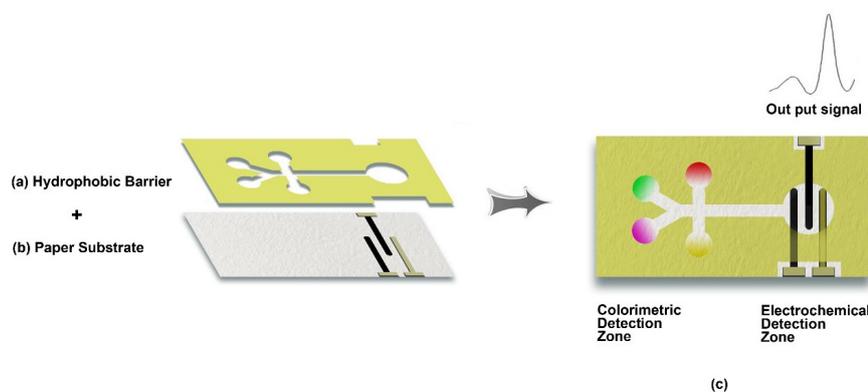


Fig. 1. Schematic presentation for the construction of a dual-detection potential microfluidics paper-based analytical devices (μ PADs). (a) The patterning of appropriate wax on the paper. (b) The paper substrate. (c) The completed μ PAD with dual colorimetric and electrochemical detection methods.

become very popular and user-friendly devices in the near future. Taken all, it should be highlighted that the μ PADs will change the path of the pharmaceutical research and development and medical sciences in the very near future, opening a new horizon in drug discovery and diagnosis.

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Ethical statement

There is none to be declared.

Competing interests

No competing interests to be disclosed.

Authors contribution

AAA, MRM and YO gathered the data and drafted the manuscript. YO finalized the manuscript.

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