CHAPTER

25

Recent Trends in the Development of Paper-Based Diagnostic Chips for the Detection of Human Viruses

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OUTLINE

25.1 INTRODUCTION

Viruses are infectious pathogens that are dangerous to human health. They can amplify infections by consuming the replication machinery of the host and using it to replicate rapidly (Liu and Gu, 2011). Annually, as many as 1 million people die due to infectious

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diseases like acquired immunodeficiency syndrome (AIDS), tuberculosis (TB), malaria, Zika virus, Ebola, HIV, and influenza (Morens et al., 2004; Bissonnette and Bergeron, 2010). Increasing death rates have forced the efforts for the development of effective clinical diagnostics. Rigorous and accurate analysis diagnoses of laboratory results guarantee successful clinical management of diseases and help to control infections in the early stage. The diagnostic kits used in the laboratory depend on various performance and operational parameters such as accuracy, sensitivity, precision, and specificity (Lalkhen and McCluskey, 2008). The WHO has set up certain criteria for diagnostics in point-of-care (POC) settings such as the affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free and deliverable to end users (ASSURED) criterion. Instant results and rapid recording of disease statuses are necessary to develop diagnostic devices (Souf 2016). To overcome the current requirements, paper-based sensors have gained much momentum in the sensor technology field.

The development of rapid, inexpensive point-of-care and easy-to-use diagnostic assays is urgently needed in multiple disciplines, including virus sensors, environmental monitoring, and clinical diagnostics applications. Among these, paper-based and flexible-material-based sensors seem to be the forerunners in sensor technology field (Shafiee et al., 2015). Paper-based sensors were introduced in the seventeenth century for colorimetric detection of uric acid through silver-based filter paper (Schiff, 1866). Over the following years, a few other applications including the detection of glucose in urine and cadmium were published (Bayley, 1878; Oliver, 1883). Despite these early implementations, it was only from the 1940s to 1990s that the next generation of paper-based analytic devices gained prominence with developments in chromatography and analytical chemistry (Ahmed et al., 2016). Microfluidic technology has gained precedence in developing point-of-care diagnosis through advanced sensor kits (Hawkins and Weigl, 2010). The popularity of microfluidic paper diagnostic devices increased as it was cost-effective, easy to use, and disposable. Currently, research focused on paper-based platforms, which use colorimetric, fluorometric, and electrochemical approaches, involves diagnosing through the signal received from the analyte (Shafiee et al., 2015). To enhance the sensitivity of paper-based analytic devices, nanoparticles including AuNPs, AgNPs, carbon NPs, liposome, magnetic NPs, and QDs have been used in combination with enzymes and other materials (Lopez-Marzo and Merkoci, 2016).

Molecular technology platforms are critical for the detection of viruses and other targeted pathogens. Nuclear acid testing (NAT) is prominent in molecular technology, as it promises rapid functioning, sensitivity, and selectivity over other methods. With the increase in the spread of infections, a low-cost and easy-to-perform alternative is urgently needed for diagnosis. Due to the limitations of other conventional methods, paper-based NAT was developed for the detection of viral and other diseases (Martinez et al., 2013; Akhtar et al., 2011). Integrated chip-based biosensors have emerged and seem to be highly potential in overcoming the limitations of the POC settings observed with NAT. These microfluidic devices can reduce the cost and amount of liquid, samples, and reagents used. Therefore, the cost of manufacturing devices is solely based on paper, glass, silicon, and polymers (Kumbhat et al., 2010).

In this review, we highlight the advances that the new-generation paper-based diagnostic devices developed in the recent years offer. Herein, we explain multifabrication of paper-based devices for the detection of viruses. The performance of the paper based on its

shape and geometry is also discussed. Device fabrication and its methodology and configuration are discussed by considering the analytic detection, the limit of detection, and the technologies used for developing these devices. Moreover, we present an overview of the performance of paper-based devices in the research field.

25.2 IMPORTANCE OF PAPER-BASED SENSORS

In the last few years, interest in paper-based sensors has gradually increased. Paper has become one of the potential materials for fabricating bioanalytical sensors due to its wide availability, hydrophilic nature, and affordability. Beyond these well-known benefits, paper has been endowed with other possible functionalities as well, owing to its physical characteristics (Martinez et al., 2013). Moreover, its high surface-to-volume ratio, porous structure, and less volume requirement are the main reasons for the surge observed in the development of paper-based sensors (Wang et al., 2012). Analyses of blood samples can be performed within a 16 min window, in contrast to the time taken by other methods. Portable enzyme-linked immunosorbent assays provide faster results than the other current and relevant techniques. Moreover, using paper-based sensors (0.1 cents/dm^2) is less expensive than the implementation of other techniques like polyethylene terephthalate and is much cheaper than glass substrates (Nery and Kubota, 2013).

Apart from the cost of devices, the development and marketing is also easier than that of other methods. In addition, it requires less investment when introduced in the market; thus, it not only is useful in the scientific community but also can be applied in practical life (Zhao and van den Berg, 2008). Compared with other substrates like glass, silicon, and PDMS that have a low surface profile, paper provides a moderate surface profile. Moreover, paper-based devices have more flexibility than other substrates. In fluid flow reaction, the capillary action takes place in paper-based sensors. Sensitivity to moisture is also a possibility in paper-based sensors, but not in other substrates; moreover, functionalization with paper is easy to achieve than other substrates (Nery and Kubota, 2013). These are some important comparisons between paper-based sensors and other techniques and fabrication methods.

25.3 DEVELOPMENT OF PAPER-BASED SENSORS

The selection of paper is based on the fabrication steps required in developing the device and certain application areas. In the research field, filter paper and certain other paper-based devices are mainly used in the microfluidic technology and for developing the sensor. In contrast, a hydrophobic nitrocellulose membrane is suitable for nonbinding biomolecules, DNA, proteins, and other molecules (Liana et al., 2012). This membrane is smooth and has a uniform pore size, allowing for more stable results. Glossy paper-based devices are also reported as suitable sensing platforms. Due to the flexible, nondegradable, and relatively smooth surface, many nanomaterials were modified with nanomaterials for better sensing (Arena et al., 2010). Paper-based substrates and appropriate detection techniques in virus sensors are summarized in Table 25.1.

TABLE 25.1 Recent Studies on Paper-Based Sensors in Detection of Viruses

Substrate	Sensing Technique	Target	Advantages	Reference
Whatman paper-wax printer	Paper-based electrochemical sensor	Hepatitis B virus	Detection limit is 85 pM. It is user-friendly, and the cost of the device is $0.36	Li et al. (2015)
Cellulose paper	Electric and optical sensing	Human immunodeficiency virus-1	Can detect multiple biotargets selectively, with sensitivity and repeatability	Shafiet et al. (2015)
Lateral flow test strip	Nucleic acid lateral flow assay	Human immunodeficiency virus-1	LOD is 0.1 nM	Hu et al. (2013)
Handmade-hydrophobized paper	Electrochemical detection	Influenza virus	LOD is 113 PFU mL^{-1} within 30 min	Devarakonda et al. (2017)
Neutravidin-modified paper	Fluorescence-based assay	Epstein-Barr virus (EBV) RNA	LOD is 5.0×10^5 cells. Total cost is approximately $1.46.	(Zhang et al. (2017)

25.3.1 Fabrication and Patterning

Paper-based device fabrication requires low-cost, easy-to-use, and efficient production processes. There are several techniques and processes available for the modification and development of these devices (Li et al., 2012). Fig. 25.1 represents the different fabrication techniques involving paper-based devices. Some of these techniques reported include analog methods, etching, plasma treatment, screen printing, laser treatment, wax printing, inkjet printing, and paper cutting. The uses of these techniques are based on the material type and applications (Liana et al., 2012). Nowadays, cellulose-fiber-based materials and nitrocellulose-based paper materials are also widely used in the fabrication of point-of-care testing. The device effect and behavior efficiency are determined by the porosity and the surface chemistry of the materials. The high fluorescence-based diagnostic assay led by fluorescent molecules and selective polymeric additives was added to commercial paper (Wong and Harley, 2009).

For paper-based device fabrication, the paper device is designed to contain a hydrophilic pattern, as hydrophobic walls enable the easy flow of liquid onto the device. The main role of the pattern is to avoid the spreading of liquid in undesired areas, reaction with specific detection areas, or parallelization of multiple reactions in a single device. Photolithography is often used to make paper-based devices through an inkjet printer, a photocopying machine, and even a hand drawing based on the UV exposure. By this method, patterning and etching of gold nanoparticles on the silicon substrate do not require clean room facilities (Kane et al., 2006). Recently, printing has involved microchannel fabrication of paper-based devices by using different types of materials (Ahmed et al., 2016). Wax printing is an advanced technique in paper-based devices that prints solid wax on top of the paper and allows the wax to melt and spread on the surface of the paper (Dungchai et al., 2011). This process overtakes the hydrophobic barriers, fluid reservoirs, and reaction area from a computer design.

FIG. 25.1 Different fabrication methods involved in paper-based devices.

The fabrication and patterning of paper-based devices can be extended to 3-D microfluidic systems. The major advantages of 3-D systems include carrying out many assays, samples that penetrate through the z direction first and then enter the x and y directions and perform multiple assays in parallel. Fabrication methods also involve adsorption, covalent modification, and entrapment, while transduction systems include colorimetric transduction, plasmonic transduction, and electrochemical transductions (Ahmed et al., 2016). For a virus sensor, research is currently directed toward modification of the device by multifunctional materials, and the combination of one or two transduction methods has great potential in the field of sensing.

25.4 MICROFLUIDIC PAPER-BASED NUCLEIC ACID TEST FOR VIRUS SENSORS

Rapid nucleic acid detection is conducted by the LFA format. However, without sample preparation, these devices are not able to detect the nucleic acid in raw biological samples (Mao et al., 2009). To eliminate the risk in other fabrication methods, the paper-based nucleic

acid device holds great prominence in the field. Paper-based microfluidic devices are developed to extract the DNA conjunction with direct detection of nucleic acid by using mobile phones (Fronczek et al., 2014). Extracted nucleic acid is undetectable by existing methods due to the presence of fewer samples. Therefore, nucleic acid amplification is necessary for NAT (Niemz et al., 2011; Craw and Balachandran, 2012). Reagent storage plays an important role in the amplification of the nucleic acid sensor. Porous materials are capable of storing large amounts of reagents in the dry form over a longer period (Stevens et al., 2008). Paper with large pores can capture molecules in its dried form and activated by addition of samples (Chong et al., 2013).

The recombinase polymerase amplification (RPA) technique, with paper-based devices, is a quick and simple alternative method to PCR. The RPA method depends on the enzymatically driven primer annealing process but does not rely on the temperature-primer annealing process (Lillis et al., 2014). In addition to RPA, LAMP has proved to be one of the most effective techniques for POC testing. LAMP provides a better production rate and is at least a hundred times more efficient than PCR. However, LAMP requires high heating power to attain a high level of amplification. Recently, we learned of the development of noninstrumented nucleic acid amplification (NAA) (LaBarre et al., 2010). In POC settings, HAD and SAMBA have also been identified as alternative techniques for NAA.

25.5 SENSING TECHNOLOGIES USED IN VIRUS SENSORS

Various paper-based analytic sensors, such as colorimetric, electrochemical, and chemiluminescent, have been developed to quantify virus detection. In this section, we will discuss the sensing mechanism and techniques involved and understand how these sensors were developed in this paper.

25.5.1 Colorimetric Sensor

A microfluidic paper-based analytic device has the ability to provide a semiquantitative or "yes/no" answer in colorimetric detection. Colorimetric sensors provide answers based on the interaction between the target substance and chemical reagents. The results of the colorimetric sensor can be viewed through direct observation using the naked eye and through computer software; the latter is a preferred mode of receiving data (Liana et al., 2012). Rodriguez et al. (2016) developed a paper-based colorimetric sensor for the detection of HVP 16 DNA. For this method, they used paper and pressure-sensitive adhesive sheets to extract, detect, and amplify nucleic acid from clinical samples. A similar type of sensor has been developed to detect HIV-1 and other pathogens by Shafiee et al. (2015).

The highly sensitive and specific colorimetric sandwich immunoassay model was fabricated for the detection of influenza A H1N1 and H3N2 viruses. The developed sensor offered benefits such as shorter processing time (around 1 h), fewer samples, and lower reagent volume used (5 μL) (Lei et al., 2015). The combination of RT-PCR and the PFMA-based colorimetric assay provides a simple and convenient diagnostic tool for the detection of viruses. The detection of influenza viruses, such as H1N1, H3N2, and H5N1, is with the

detection limit of 10^2 copies (Kim et al., 2014). Recently, a single-stranded DNA, hybridized with gold nanoparticles, was developed for the detection of TB DNA at a concentration of 2.6 nM. Due to DNA hybridization, a color change of red to blue occurred. Since this sensor operated through a mobile phone, the results of color change and accompanying data were transferred via computers (Tsai et al., 2013).

25.5.2 Electrochemical Sensor

Electrochemical detection is suitable for microfluidic PAD as it is cost-effective, user-friendly, highly sensitive and selective, and low on electrical consumption. Most electrochemical sensors were developed to detect glucose, uric acid, and molecules. The basic working principle of an electrochemical sensor is based on the electric current, which is produced from the chemical reaction, passed through the electrode (Dungchai et al., 2009; Yetisen, 2015). The hollow channel SlipPAD methodology and electrochemical-based sensor were developed for the detection of HBV virus. The obtained LOD is 85 pM and costs $0.36, comparably lower than earlier detection methods. However, some problems did occur during the implementation of the system, which included reagent resolvation, time management issues in the hybridization step, and nonspecific adsorption (Li et al., 2015).

Graphene-polyaniline-modified paper-based electrochemical biosensor was developed by the inkjet printing technique for the detection of human papillomavirus (HPV). By electrochemical impendence spectroscopy, the efficiency of the sensor was measured. The results showcased a detection limit for the HPV type 16 DNA to be 2.3 nM with a linear range of 10–200 nM. The advantages of this sensor include cost-effectiveness, ease of use, and disposability (Teengam et al., 2017). Narang et al. (2017) fabricated an electrochemical paper-based device for the detection of herpes caused by the herpes virus 5 (HHV-5) DNA through the integration of Zn-Ag nanoblooms with a detection limit of 97 copies per mL. The device was cost-effective, user-friendly, and simple.

25.5.3 Electrochemiluminescent Sensor

Electrochemiluminescence (ECL) is the combination of chemiluminescence and electrochemical techniques that results in the generation of light. Dynamic concentration response and sensitivity, the requirement of fewer samples, and easy handling are the major advantages of ECL. More than 150 different types of immunoassays are available in the market for the detection of tumor and infectious diseases (Ge et al., 2012; Parveen et al., 2013).

ECL has gained widespread attention owing to its performance in the rapid detection of viruses. A novel paper-based ECL biosensor was developed for hepatitis B. This sensor showed high sensitivity, selectivity, and reproducibility. It performed better at a detection limit of 34.2 pg/mL to 34.2 ng/mL (Chen et al., 2018); however, the process is time-consuming. By using the PCR technique, the viral RNA of a dengue virus from dried blood samples was developed. We concluded that the major benefit recognized from this study was that the dengue RNA was highly stable, allowing it to be stored and transported in laboratory condition (Prado et al., 2005).

25.5.4 Enzyme-Linked Immunosorbent Assay

Microfluidic paper-based analytic devices have great potential to transform conventional immunoassays for diagnosis. Mu et al. (2014) developed a multiplex microfluidic paper-based immunoassay device for the detection of human igG antibody against HCV. They fabricated the device for multitest zones with highly flammable nitrocellulose, patterned by craft punch patterning. With this device, the LOQ of a mouse igG in chemiluminescence and colorimetry is set at 267 amol and 26.7 fmol, respectively. Pardee et al. (2016) developed a freeze-dried paper-based sensor for the detection of Zika virus by the combination of nucleic-acid-based molecular diagnostic and RNA amplification. The developed sensor employed the simple preparation of extracting the viral RNA, thus, demonstrating the robust detection of a Zika virus. In this sensor, the enzymes are combined with engineered gene circuits and freeze-dried on the paper. Further, a sensor for mRNA Ebola virus was developed, which was fabricated in 12 h and possessed a DNA input of the Ebola series, with a cost of $21 per sensor (Pardee et al., 2014). A magnetoelastic (ME) sensing system comprises a test paper for the detection of classical swine fever virus (CSFV). The anti-CSFV is immobilized on the ME surface and developed using ELISA analysis, which provided detection with a sensitivity of about 95 Hz/μg/mL and a limit of 0.6 μg/mL (Guo et al., 2016). Rohrman and Richards-Kortum (2012) used micro-PADs for the enzymatic amplification detection of the HIV DNA. This technique successfully enhanced the 10 copies of the HIV DNA within 15 min. Fig. 25.2 represents the schematic for the ELISA method.

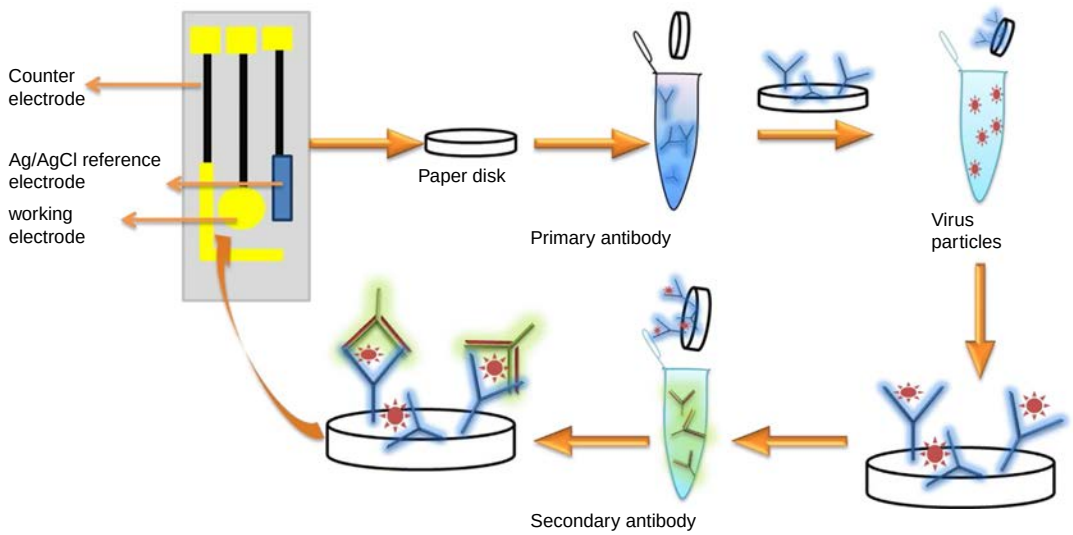

FIG. 25.2 Schematic diagram of ELISA for virus sensor.

25.5.5 Amplicon Detection in Paper-Based Diagnostics

Amplicon, including amplicon HIV-1 and HIV-1 QT, is a piece of DNA or RNA that makes it possible to analyze viruses using different techniques. Following nucleic acid amplification, a unique technique is required for the detection of amplicon. Gel electrophoresis and fluorescent detection methods are complicated, require costly equipment, and use chip-based detection techniques, creating difficulty in device fabrication (Ahmad and Hashsham, 2012; Hu et al., 2013). Single-stranded commercial DNAs are mostly used in LFA techniques. While double-stranded amplicon DNA is available and can be bound to a complementary DNA probe. A double-stranded DNA amplicon can be detected by Ag-Ab interaction. Gold nanoparticle-amplicon conjugates the binding of digoxigenin Ab on the test line, and results showed positive signals, with immobilized anti-rabbit Ab acting as a control (Kersting et al., 2014).

Metal nanoparticles are also used in the sensitivity process of LFA with thermal contrast. Upon irradiating with laser light, the metal nanoparticles released heat and helped in producing a colorimetric signal with 36 folds (Qin et al., 2012). Several fluidic control techniques are developed using paper architecture modifications and wax-printed pillars. Microfluidic paper-based analytic devices are also used as an amplicon sensor. Based on the biotin-streptavidin interaction, an instant paper-based device was fabricated using wax printing techniques for the detection of LAMP (Lo et al., 2012). The benefits of a paper-based system for NAT include cost reduction, simplicity of data, and aptness of device fabrication for POC applications. With the excellent capability possessed by paper-based platforms with advanced technology and fabrications, we expect more paper-based devices to be developed to overcome the drawbacks in the present techniques.

25.6 LIMITATIONS OF PAPER-BASED DIAGNOSTICS

Paper-based analytic devices provide cost-effective solutions in the viral sensor field. These are preliminary screening tools for health care and are useful and user-friendly (Whitesides, 2013). However, the paper-based sensor needs further improvement with respect to its cost base and clinical performance. Previously reported papers show varying ranges in the sensitivity and specificity of all its aspects (Pike et al., 2013). However, the main disadvantages observed include the following: First, different substrates and detection methods can be attached in different combinations to develop the sensor, and the cost depends on the fabrication sensor (Millipore, 2013); second, controversial readouts are reported due to subjective judgments by the operators and illumination settings, especially in the colorimetric sensor; third, environmental effects play a major role in the upkeep of the testing devices; and finally, batch-to-batch variation is a well-known challenge in POC testing (Abe et al., 2010; Li et al., 2011) and affects this method of diagnostics. Therefore, paper-based diagnostics will need to improve with respect to its sensitivity and selectivity for widescale clinical applications.

25.7 CHALLENGES AND FUTURE OUTLOOK OF PAPER-BASED CHIPS

The paper-based device has enormous potential in the sensor field. However, more development is required so that its performance match that of conventional analytic techniques. Through synergies with materials science and biomedical engineering, paper-based diagnostics are becoming simpler, more accurate, and more sensitive. The sensitivity has increased due to the distance between the sample loading in the paper and the detection zone. The analyte is spread across the paper; the concentration of the sample may decrease due to evaporation if the distance of the sensing zone and sample loading region is large. Evaporation of the sample can be addressed by modifying the paper using sticky tape or porous substrate (Apilux et al., 2010). Current research provides a high-level epidemiological monitoring of viral diseases. However, it is without question that we need to amplify public health ambitions and invest in the development of diagnostic methods, reduce cost, and bring about size-based improvements (Loman et al., 2012; Frey et al., 2014). Microfluidic technology is a prominent piece of the modern diagnostic system that includes biomedical research, DNA analysis, environmental sensor, and food safety (Sher et al., 2017). These devices can become the future of sensing kit options, even though they are currently facing some limitations such as low sensitivity and reproducibility, and the current paper-based microfluidic devices have limited capabilities in the sensor chips.

Paper-based diagnostics, mobile-phone-based optical detection, and telemedicine have gained more importance in terms of improving health-care diagnostics tools. However, limitations such as plasma separation, sample pretreatment, nucleic acid isolation, and amplification hinder their potential in POC diagnostics (Hu et al., 2014). These aspects are important in paper-based diagnostic devices with respect to sensitivity and selectivity. Lab-on-a-chip (Cao et al., 2012) is a small device that consumes small amounts of samples to perform immediate reactions with sensing devices. The reactions vary as per our analyte, detection method, and instruments. LOC devices are approved by the FDA to feature among the diagnostic devices for influenza, HIV, and HVB (Alyassin et al., 2009; Cao et al., 2012; Zhi et al., 2014). The recent developments in paper-based diagnostic devices are reconstructing clinical microbiology and the role of detection methods in reducing the prevalence of infectious diseases.

In conclusion, we described the basic concepts and developing methods and have highlighted paper-based diagnostic devices applied in the last decade in the virus-sensing field. The fundamentals, device fabrication, functionalization, and different techniques used in the paper-based devices have been critically discussed. This review also provides the advantages and disadvantages of current paper-based diagnostic devices and discusses development trends for the future. Owing to new advancements in nanotechnology, paper-based sensing rises above alternative methods for the development of rapid diagnostic sensors for food safety, environmental control, and personalized medicine.

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