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Review

Inkjet-Printed and Paper-Based Electrochemical Sensors

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Featured Application: Low-cost point-of-care diagnostics.

Abstract: It is becoming increasingly more important to provide a low-cost point-of-care diagnostic device with the ability to detect and monitor various biological and chemical compounds. Traditional laboratories can be time-consuming and very costly. Through the combination of well-established materials and fabrication methods, it is possible to produce devices that meet the needs of many patients, healthcare and medical professionals, and environmental specialists. Existing research has demonstrated that inkjet-printed and paper-based electrochemical sensors are suitable for this application due to advantages provided by the carefully selected materials and fabrication method. Inkjet printing provides a low cost fabrication method with incredible control over the material deposition process, while paper-based substrates enable pump-free microfluidic devices due to their natural wicking ability. Furthermore, electrochemical sensing is incredibly selective and provides accurate and repeatable quantitative results without expensive measurement equipment. By merging each of these favorable techniques and materials and continuing to innovate, the production of low-cost point-of-care sensors is certainly within reach.

Keywords: electrochemical sensor; inkjet printing; paper; carbon nanomaterials; flexible electronics

1. Introduction

In a world where new technology is introduced regularly, innovation is critical to advancement. A multitude of motivations drive this constant innovation ranging from convenience to resource limitations. In fact, one of the primary driving forces behind modern innovation is cost. In order to reduce production cost, there are two traditional paths that can be taken. In both cases, cost reduction ultimately requires developing or altering materials, methods, or processes as well as developing or obtaining new equipment. The first path involves the development of new materials or processes to further reduce cost. Of course, this preliminary development phase will likely increase cost initially, but in the long-term, more advanced materials and techniques will eventually save money. The second path involves the utilization of existing technologies including readily available materials, well-defined processes, and established equipment. By employing these existing solutions and applying them to a new field or application, both development costs and production costs can be reduced substantially.

As it applies to sensor development, this continuous pursuit of cost savings has driven incredible innovation, allowing for the production and distribution of sensing devices and platforms at an affordable price. Of course, many other sensor requirements drive advancement including sensitivity and size, but it has become increasingly more important to introduce low-cost point-of-care sensing solutions to the market. In many cases, time is critical, and transporting samples to a remote laboratory may be very time-consuming and even result in sample contamination. On the other hand,

the ability to transport small portable sensing devices to the field is a critical advancement allowing for a much simpler process that maintains sample integrity while improving efficiency.

To meet this ever-increasing need, some research groups have focused on new materials and methods, while others have relied on tried-and-true materials, methods, and equipment. Given the notable results and advancements in this field, the latter of these approaches remains the focus of this review article. The use of existing technologies has allowed the production of many exemplary devices capable of being used in a point-of-care situation. In particular, among existing fabrication technologies, printing has become incredibly popular due to its ease of use and low-cost equipment. Although various printing methods have been investigated and demonstrated, inkjet printing has many advantages that lend itself particularly well toward the development of low-cost point-of-care analytical devices.

Furthermore, with respect to materials, the use of paper to develop sensing platforms has gained significant attention in recent years due to its exceptional mechanical properties, porous structure, low cost, and natural origin [1–4]. Considering the wide applications of microfluidics in point-of-care diagnostics, environmental analysis, and food processing, utilizing paper in microfluidic systems can overcome the limitations caused by conventional materials including glass, polydimethylsiloxane (PDMS), and silicon. Paper is both biocompatible and biodegradable, which opens the door for potentially disposable paper-based devices capable of chemical and biological sensing. Additionally, paper has a natural ability to wick fluids, enabling the fabrication of pump-free microfluidic paper-based analytic devices (μPADs) [4–6].

The concept of guided fluid flow inside paper was first introduced by Muller et al. for chromatography applications in 1949 [7]. However, the Whitesides group at Harvard University first reported employing paper in microfluidics in 2007, where they presented the first paper-based microfluidic device with millimeter-sized channels fabricated using photolithography [8]. As a result of the prototype produced by this particular group, it became apparent that paper-based sensors can indeed be fabricated using simple processes that yield disposable devices for point-of-care diagnostics. Following this publication, a number of other groups demonstrated the ability to pattern paper-based substrates using hydrophobic materials. In addition to photolithography [8,9], other methods capable of producing paper-based microfluidic devices include plasma treatment [10], wax printing [11,12], inkjet printing [13–19], and screen printing [5,11,12,20–28]. Among these patterning methods, wax printing has been the most frequently used method to develop microfluidic paper-based analytic devices (μPADs) [11,12,22,29].

Since the emergence of paper-based sensors, various sensing mechanisms have been utilized [30]. The most popular methods demonstrated in literature include colorimetric [8,11], chemiluminescence [31], chemiresistive [32–34], and electrochemical [15,17,18,35–37] techniques. Each of these sensing mechanisms have been employed extensively to develop paper-based sensors. Although the various sensing mechanisms have their respective advantages and disadvantages, electrochemical sensing remains the most common and most effective method for paper-based devices due to its accuracy, reliability, quantitative results, and ability to distinguish between multiple analytes in a single sample. These sensors are called electrochemical paper-based analytical devices, or simply ePADs, a term coined by the Henry group in 2012 [21].

Given the substantial growth in the fields of paper-based analytic devices and printed electronics, this review article is intended to focus on the key components of each field that support the fabrication of low-cost point-of-care sensors. The collision of these two fields combines significant advantages and is paving the way towards inkjet-printed paper-based electrochemical devices for chemical and biological sensing. Such devices are low-cost, easy to manufacture, and disposable while maintaining high accuracy and sensitivity. Applications of these devices include on-site patient diagnostics, water and air pollution monitoring, cancer screening, and much more.

2. Fabrication Methods

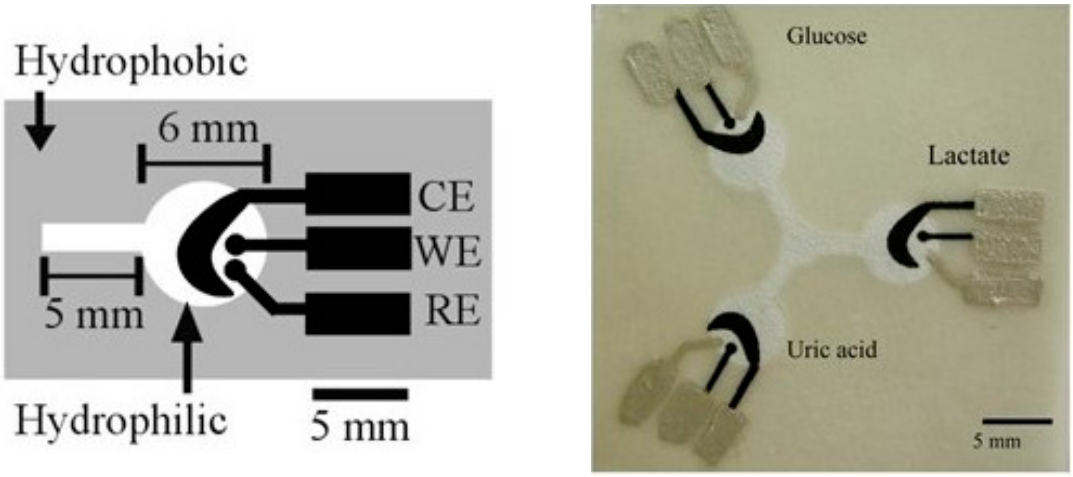
For modern electronic components and systems, an abundant number of fabrication methods exist allowing for incredible control over the process and device parameters. Depending on the needs for a particular device or system, a number of fabrication methods are considered. Parameters of interest when considering various fabrication methods include materials, deposition thickness and uniformity, device dimensions and tolerances, space limitations, and of course cost. Among the existing fabrication techniques, well-established semiconductor fabrication methods provide precise control over device dimensions, accept the usage of a large range of materials, and enable fine control over doping and other parameters. Common semiconductor fabrication methods include sputtering, evaporation, chemical vapor deposition, and photolithography. Although the knowledge and experience surrounding standard semiconductor manufacturing techniques is vast, the cost to use these techniques can be particularly high. The equipment alone is quite expensive, but many techniques require specialized facilities like cleanrooms to operate properly and produce functioning devices. Furthermore, substantial floor space is also required for many of these pieces of equipment. As a result of these requirements, it is becoming more and more common to investigate other existing fabrication methods to reduce cost.

As an alternative to standard semiconductor manufacturing techniques, a number of other methods have been explored in order to drive down manufacturing time and cost. In terms of electrode fabrication, various groups have demonstrated the use of inkjet printing [13–19], screen printing [11,12,20–25], and microwire placement [38] on flexible or paper-based substrates. In addition to electrode fabrication, some groups have also utilized various techniques for patterning fluid channels on paper using hydrophobic materials. Channel fabrication has been achieved using photolithography [8], plasma treatment [10], wax printing [11,29], inkjet printing [13], and screen printing [20]. Among these techniques, both screen printing and inkjet printing are the most prominent techniques for patterning electrodes and accompanying hydrophobic barriers. Although this review is intended to focus on inkjet-printed sensors, it is important to thoroughly review screen-printed sensors as a comparison. Both of these printing techniques are incredibly adaptable and provide a low-cost manufacturing process. However, it is the authors' opinion that inkjet printing is a superior process due to its individual advantages, which are discussed in detail in Section 2.2.

2.1. Screen Printing

Screen printing is the first and most frequently used method for fabrication of paper-based electrochemical sensors. This particular fabrication method is popular in the clothing industry where it is used to apply labels and designs to shirts and other articles of clothing. Screen printing is a relatively simple process that utilizes ink, a template or stencil, and a squeegee. The template or the screen is first designed and fabricated. Depending on complexity, the template may require computer-aided design (CAD) software for design and specialized equipment for fabrication. After fabrication, the template is placed over the substrate and long thin bead of ink is deposited along one edge of the template. Finally, the squeegee is used to spread the ink across the entire surface with constant even pressure. After removing the template, the ink is left to dry.

Among the many demonstrations of utilizing screen printing to fabricate electrochemical sensors, the Henry group at Colorado State University was the first group to incorporate electrochemical measurements in a paper-based microfluidic device [39]. In order to guide the sample fluid, photolithography was initially used to define channels and detection zones. Following photolithography, screen printing was performed in two separate steps to implement the electrodes and contacts. First, silver/silver chloride (Ag/AgCl) ink was screen-printed to define the reference electrode and contact pads. Next, carbon ink containing Prussian Blue was screen-printed to implement the working electrode and the counter electrode. The basic design and a fabricated electrochemical cell are shown in Figure 1. Using this system, they were able to measure the concentration of glucose, lactate, and uric acid.



(**a**) (**b**)

Figure 1. The first paper-based electrochemical analytical device developed using screen printing: (**a**) The basic design of each detection zone; (**b**) The fabricated sensor with three detection zones for multi-analyte detection. Reproduced with permission from [39], Copyright American Chemical Society, 2017.

Dossi et al. demonstrated an electrochemical gas sensor using paper as the supporting material for a room temperature ionic liquid (RTIL) [12]. In this work, a three-electrode electrochemical cell was fabricated on filter paper with a thermally-laminated polyethylene (PET) backing used to prevent gas permeation. Here again, wax printing is used to form a hydrophobic barrier to contain the liquid sample. Working, counter, and reference electrodes were then created by screen-printing conductive carbon ink. The carbon ink was doped with cobalt(II) phthalocyanine due to its electrocatalytic properties toward the thiol oxidation. Next, the paper was soaked in butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide as the RTIL.

Another example of an ePAD developed by screen printing was demonstrated by Rattanarat et al. [21]. This sensor was used to determine dopamine (DA) levels in biological samples. The microfluidic channels were patterned on paper using photolithography based on SU-8. Carbon-based ink was then used to screen-print electrodes to form a commercial electrochemical sensor for square-wave voltammetry. To improve the performance of the sensor, the filter paper as modified with sodium dodecyl sulfate (SDS) as the ionic surfactant, which facilitated the diffusion of DA between paper layers.

Furthermore, an ePAD was fabricated by Ruecha et al. for determination of cholesterol in human blood serum [22]. The working and counter electrodes were patterned using screen printing and carbon ink, and a Ag/AgCl electrode was used as the reference electrode. The working electrode was modified by a nanocomposite made from graphene, polyvinypyrrolidone (PVP), and polyaniline (PANi). Also, cholesterol oxidase (chOx) was attached to these nanoparticles (NPs), and the chronoamperometry measurements were performed for determining the concentration of cholesterol.

Using a unique form-factor, Wang et al. demonstrated an ePAD for determination of beta-hydroxybutyrate (BHB) levels which is a biomarker for diabetic ketoacidosis [23]. They fabricated a three-dimensional microfluidic device that can alter the fluid direction flow or electrical connection by folding the device. Each of the three electrodes were implemented using screen printing and carbon-based ink. The sensor is referred to as a "pop-up" device by the authors and was designed specifically to integrate with a commercial glucometer. Among all of the devices reviewed in this article, this particular ePAD is certainly the best demonstration of a low-cost, portable sensor for point-of-care applications. The fabricated sensor before and after folding is shown in Figure 2.

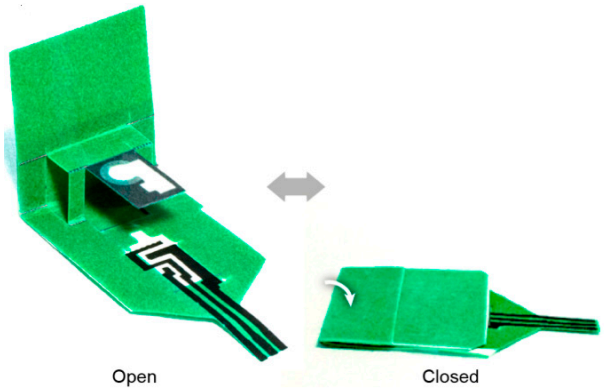


Figure 2. Pop-up paper-based sensor fabricated by Wan et al. for determination of BHB levels. Reproduced with permission from [23], Copyright American Chemical Society, 2017.

Rattanarat et al. developed a multilayer paper-based device for detection of metals, in which they used both colorimetric and electrochemical sensing mechanisms [11]. Filter paper served as the colorimetric sensing substrate and a polyester film served as the electrochemical sensing substrate. The two materials were essentially taped together to form an integrated device as shown in Figure 3. Like many of the other demonstrations, fluidic channels were defined on the filter paper using a wax printing technique. To form the reference electrode, unmodified carbon ink was screen-printed on the polyester film. To form the working and counter electrodes, a mixture of multi-walled carbon nanotubes, graphite powder, and carbon ink was then screen-printed on the same transparency film.

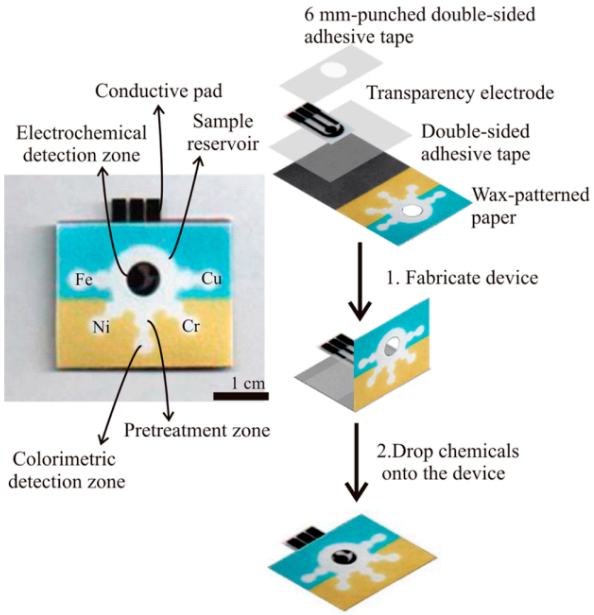


Figure 3. Fabrication process and sensor layout developed by Rattanarat et al. for metal detection. Reproduced with permission from [11], Copyright American Chemical Society 2017.

Apilux et al. have also combined colorimetric and electrochemical techniques to enable simultaneous detection of gold and iron [24]. They patterned the microfluidic channels and detection zone using photolithography with SU-8 as the photoresist. The working and counter electrodes were screen-printed using carbon ink, and Ag/AgCl ink was utilized to fabricate the reference electrode. The fabricated sensor is shown in Figure 4.

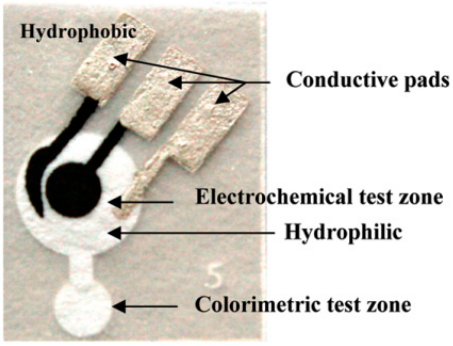


Figure 4. The fabricated Au(III) sensor with a three-electrode electrochemical setup and colorimetric detection zone for determination of Fe(III). Reproduced with permission from [24], Copyright American Chemical Society, 2017.

The porous structure of paper and its low cost make it a desirable candidate for immobilization of enzymes on the electrodes surface. Yang et al. have used this advantage in order to develop a paper-based glucose sensor [25]. Unlike the other groups working on ePADs, this group purchased and modified a commercially available screen-printed paper-based electrochemical sensor. The working electrode was modified with platinum (Pt) nanoparticles using an electrodeposition method in order to facilitate electron transfer at the surface of the electrode. To fabricate the sensor, they soaked paper in a glucose oxidase solution to achieve an enzyme-modified paper. Next, the modified paper was placed on top of the electrode and fixed in place using a plastic holder. The mechanical properties of the enzyme-modified paper were investigated, and the results indicated that the modified paper was tougher than the unmodified paper.

As demonstrated by each of these example devices, screen printing is a very suitable fabrication technique to use in developing low-cost paper-based sensors. The design and manufacturing process is relatively simple and does not require significant knowledge to execute. Despite these advantages, screen printing is not necessarily the best choice in all cases. For instance, through the screen printing process, a large volume of material is required, which may limit the application of this method when using expensive electrode materials such as noble metals. Moreover, this method requires a stencil to pattern the electrodes, which limits the achievable maximum resolution. It is also not possible to quickly alter the stencil. Furthermore, the pressure applied during the fabrication process will increase the clogging possibility of the paper pores, which could impede fluid flow in paper-based microfluidic devices. As will be discussed in the following section, inkjet printing has multiple advantages over screen printing that, when utilized properly, yield a notably superior fabrication technique.

2.2. Inkjet Printing

Inkjet printing is a very well-known deposition technique due to its prevalence in home and office environments across the world. As a result of its popularity, inkjet printing is a very low-cost technique lending itself toward fabrication of paper-based electrochemical sensors with distinct advantages. Unlike screen printing, inkjet printing does not require the pre-fabrication of a template or stencil. Instead, the pattern is designed using CAD software and sent directly to the printer which is able to precisely deposit very small ink droplets row by row to form the desired two-dimensional shape. Furthermore, due to the nature of the deposition technique, inkjet printing allows for greater control over the pattern as compared to screen printing through the selection of different printing equipment. For example, in low budget circumstances, regular office printers can be modified to be used with custom ink for paper-based electrochemical sensor fabrication [15,40]. On the other hand, when greater precision and control are required, sophisticated material printers are available that allow for precise adjustment of ink droplet volume, ejection speed, and spacing. Additionally, many of the high-end printers even come with heated beds to allow for better control over ink dry times. As an example,

the FUJIFILM Dimatix Materials Printer is a very capable inkjet printer that enables incredible control over the printing process.

Given these advantages, inkjet printing has been used by many groups to fabricate paper-based microfluidic analytical devices. One of the first paper-based electrochemical sensors was developed by Maattanen et al. [14]. A piezoelectric commercial printer (Dimatix Materials Printer) and silver and gold ink were employed to pattern electrodes on a paper substrate. Additionally, a AgCl layer was electrochemically deposited on silver strips to achieve a Ag/AgCl reference electrode. Lastly, a reaction well was formed on the paper platform using PDMS. Various electrode modifications were performed on the sensor in this report including electropolymerization of a polyaniline film on the working electrode surface using cyclic voltammetry in order to develop a potentiometric pH sensor. Furthermore, a glucose biosensor was developed by modifying the electrode surface with glucose oxidase. The schematic diagram of the paper-based sensor developed in this work is illustrated in Figure 5.

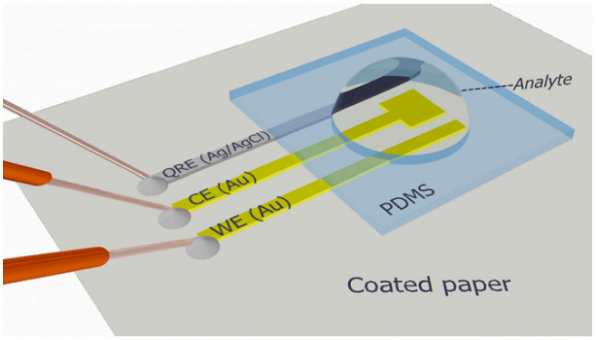


Figure 5. The schematic diagram of the inkjet-printed electrochemical sensor on paper developed by Maattanen et al. Reproduced with permission from [14], Copyright Elsevier, 2017.

Another well-executed demonstration of a fully inkjet-printed paper-based electrochemical sensing platform was presented by da Costa et al. in 2015 [15]. Custom-made carbon ink based on multi-walled carbon nanotubes was achieved by using SDS as an ionic surfactant. Next, the ink was transferred into a commercial cartridge, and the three-electrode electrochemical sensor was printed onto a paper substrate by employing a standard office inkjet printer. The printing process was repeated several times in order to yield electrodes with a lower sheet resistance. Additionally, mineral oil was printed onto the substrate to act as a hydrophobic barrier during sensing. The fabrication process and the schematic diagram of the sensor is depicted in Figure 6.

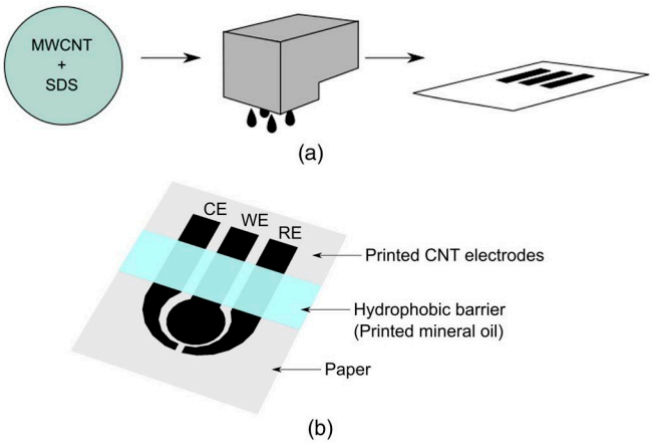


Figure 6. Illustration of the fully inkjet-printed electrochemical sensor developed by da Costa et al.: (**a**) Fabrication process; (**b**) Schematic diagram of the completed sensor. Reproduced from [15].

Shamkhalichenar and Choi also reported an inkjet-printed paper-based electrochemical sensor fabricated using carbon nanotube ink and Ag nanoparticles as an electrocatalyst for hydrogen peroxide detection [17]. In order to increase the conductivity of the inkjet-printed electrodes, a sintering process was employed.

Lessing et al. presented two notable contributions to fully inkjet-printed paper-based sensors through the use of an embossed well and chemically modified paper [41]. Unlike many of the other groups utilizing hydrophobic materials, this particular group chemically altered the paper prior to printing. Specifically, through a simple process, they were able to develop what is referred to as omniphobic "fluoroalkylatd paper" ("R^F paper"). This treated paper is essentially hydrophobic and oleophobic, which still allows it to absorb fluids but yields a very large contact angle with ink droplets. As shown in Figure 7, this results in a much higher resolution print. In addition to chemically modifying the paper substrate, this group also physically altered the shape of the paper through an embossment process in order to produce a reservoir for the sample. To form the working, counter, and quasi-reference electrodes, they employed a piezoelectric inkjet printer and carbon-based ink. Furthermore, a repeatability demonstration was performed using multiple fabricated sensors yielding very little variation in the measurements. This is actually a very significant conclusion for inkjet-printed paper-based sensors. Due to the nature of the fabrication technique and the substrate material, there are sincere concerns over repeatability across mass-manufactured devices. Although additional demonstrations are required to support these results, the paper treatment and subsequent printing certainly indicate that high-resolution repeatable patterns are possible with paper-based substrates.

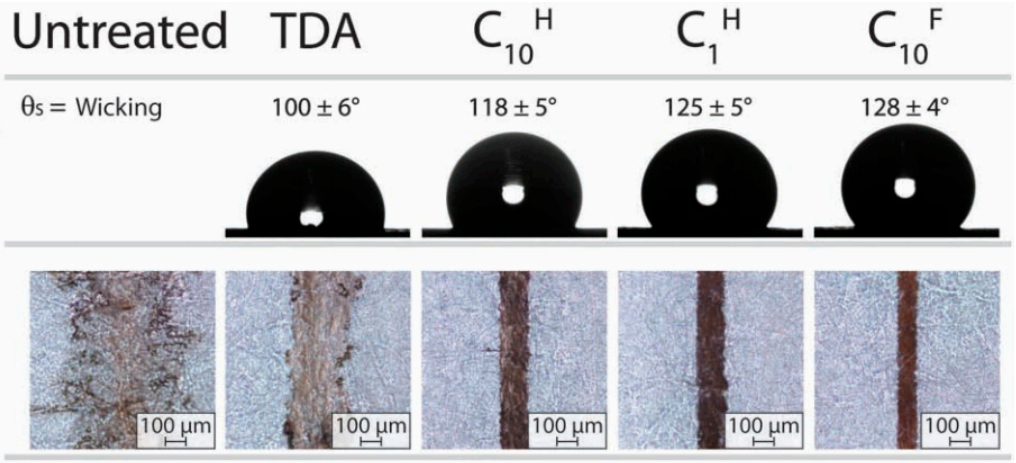


Figure 7. Demonstration of change in ink contact angle and print resolution due to chemical modification of the paper substrate by Lessing et al. Reproduced with permission from [41], Copyright Wiley-VCH, 2017.

Another more basic method to achieve high-resolution prints was utilized by Hu et al. [42]. Instead of modifying the paper substrate, this group opted to use a standard home photo printer with a compact disc (CD) slot. Unlike simple home printers for common documents, the Epson R230 inkjet printer used by this group is specifically designed to produce high quality photo prints that maintain a high resolution. The fabrication process included two primary steps. First, gold nanoparticles were printed onto a paper substrate. Next, the substrate was placed into a plating solution for seeded growth. This produced high-resolution electrochemical sensors with good conductivity. In the final fabrication step, a drop of 1-butyl-3-methylimidazolium hexafluorophosphate ($BMIMPF_6$) was placed on the sensing area and allowed to dry, resulting in a novel paper-based electrochemical oxygen sensor.

Deviating from the norm, Kit-Anan et al. recognized advantages of both screen printing and inkjet printing, which led to a device fabricated using both deposition techniques [43]. Screen printing was first used to form the working, counter, and reference electrodes using carbon-based ink. Next,

inkjet printing was used to deposit polyaniline on the working electrode for detection of ascorbic acid. This is an interesting approach that demonstrates the flexibility of inkjet printing. Without any need to fabricate a stencil or template, multiple ink cartridges can be loaded with various functional materials aimed at detecting distinct target analytes.

As demonstrated by these examples, inkjet printing is a simple but sophisticated fabrication method that is very well-suited towards paper-based sensors. Thus far, screen printing has arguably been the most popular method of fabrication for paper-based sensors, but inkjet printing is quickly gaining popularity. When compared to screen printing, inkjet printing has a number of notable advantages including incredible control over material thickness as well as the ability to deposit multiple materials simultaneously. Additionally, inkjet printing does not require fabrication of templates or the administering of post-printing steps.

3. Ink Materials and Requirements

Among the various considerations within inkjet printing, the ink itself is arguably the most important element and certainly requires the most attention. Selecting the proper materials and developing the ink correctly are critical in inkjet printing deposition. This is not a particularly difficult process, but it can have a significant effect on the printing process and resulting device. As a result, special care should be taken during the ink development process to ensure all needs are met. Just as printer and substrate selection exhibit their respective tradeoffs, many factors are involved with ink development including the fluid material selection, the conductive material selection and geometry, and the mixing process selection. Each of these components affect device performance and cost as well as flexibility and manufacturability.

3.1. Ink Materials

Although a multitude of materials can be deposited with an inkjet printer, inkjet-printed electrochemical sensors typically require a small class of materials, namely conductors and hydrophobic materials. Obviously, conductors are needed for electrode fabrication whereas hydrophobic materials are useful for defining microfluidic channels. Although not necessarily applicable to the field of electrochemical sensing, inkjet printing can also be utilized with semiconducting and insulating materials for fabrication of other flexible electronics. However, given the application, semiconducting and insulating materials are not necessarily useful in traditional electrochemical sensors.

Among conductors, the most common materials used are metallic nanoparticles and metallic nanowires as well as carbon-based materials such as carbon nanotubes, carbon powder, and graphene. In addition to using carbon nanotubes purely for their high conductivity, modified carbon nanotubes can also be used to enable detection of different analytes. Due to their nanometer dimensions, these materials can be dispersed in various mediums to develop nanomaterial ink capable of being deposited by an inkjet printer.

While the conductive materials are obviously required for electrode formation, these materials must be dispersed in a fluid medium to be used in the inkjet printing process. Like many other coatings, ink can either be water-based or solvent-based, each with their own respective advantages. Water-based ink is certainly much easier and safer to handle considering that solvents can be corrosive and potentially harmful if they are inhaled or make contact with the skin. However, water-based ink typically requires the addition of an ionic surfactant to disperse the conductive materials. This not only increases material cost, but it can possibly inhibit contact between the nanomaterials ultimately reducing the electrode conductivity. On the other hand, solvent-based ink is able to naturally disperse small concentrations of conductive materials without the addition of other materials. Additionally, solvent-based ink exhibits much faster dry times when compared to water-based ink. This can enhance the nanomaterial network uniformity ultimately increasing electrode conductivity. Furthermore, with a better network, fewer layers need to be printed to achieve the necessary conductivity. Given these advantages and disadvantages, it is important to consider all

of these properties when developing ink and selecting a fluid medium. Fortunately, due to the recent growth in popularity, various types of inkjet-compatible ink are readily available on the commercial market. In fact, many of the publications discussed in this review refrained from developing custom ink and instead purchased ink from a third-party source.

3.2. Ink Characteristics

In order to print properly and produce the desired printing results, the ink must maintain certain characteristics. First, the ink must be well-dispersed to avoid clogging the printer nozzle. This is typically achieved either by using solvent-based ink or by including an ionic surfactant in water-based ink. In addition to preventing clogging, well-dispersed ink is also helpful in ensuring that a uniform network is achieved after printing. The second desired characteristic for the ink is low surface tension. Because the inkjet nozzle is constructed to eject very small ink droplets, surface tension can play a significant role in the printing process. As an extreme example, high surface tension inks may not print at all. The solution to this problem actually overlaps with the dispersion problem. Typically, for solvent-based ink, no additional materials are needed since most solvents have an inherently low surface tension. However, for water-based ink, the surface tension is too high and can be reduced by adding an ionic surfactant as demonstrated below in Figure 8. The last ink property to be considered is viscosity. This is usually not an issue for solvent-based or water-based ink, but depending on the additives, the developer must ensure that viscosity is low for proper printing. With these criteria met, it is certainly possible to develop different kinds of ink and utilize inkjet printing for nearly any materials-based application.

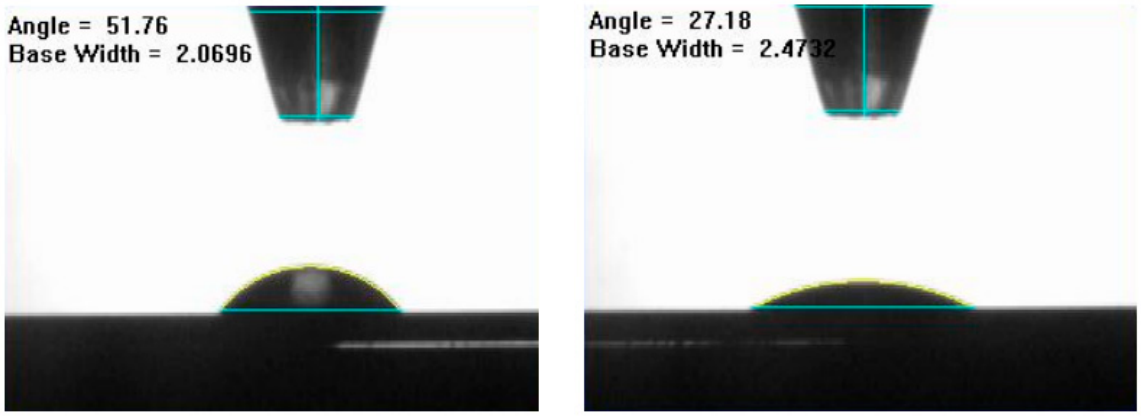


Figure 8. Demonstration of surface tension and how it can be affected with an ionic surfactant: (**a**) High surface tension ink with a large contact angle; (**b**) Low surface tension ink with a small contact angle. Reproduced from [44].

4. Electrochemical Detection and Its Applications

Among all of the paper-based biological and chemical sensors, various sensing mechanisms have been used, each with their own respective advantages and disadvantages. Although the focus of this review article is electrochemical sensing, it is important to briefly discuss other sensing mechanisms as a comparison. Each of the sensing mechanisms typically falls under two categories, namely optical detection and electrical detection. Optical detection methods include colorimetric detection, fluorescence, and chemiluminescence. Electrical detection methods include chemiresistive sensing and electrochemical detection.

As an example of optical detection, one of the simplest and most popular detection methods is colorimetric detection [8,11]. In colorimetric detection, certain chemical or enzymatic reactions

are utilized to produce a color change based on the presence of the target analyte. If the anlayte concentration is higher, the color change will be more noticeable. This method has been successfully used for the detection of proteins [45], enzymes [46], and metals [11,47]. The main drawback of the colorimetric analysis method is that the measurement results are usually qualitative or semi-quantitative, and the presence of relatively complicated optical detectors and image processing units is required. Fluorescence detection is another method that has been widely used in μPADs to detect various analytes [48,49]. The fluorescence method requires external instrumentation such as excitation light and optical detectors. Furthermore, the primary disadvantage of this method is the presence of a high background signal which originates from the chemicals used in the paper-bleaching process [4]. Yet another method demonstrated in paper-based analytical devices is chemiluminescence detection [31]. In this approach, the light intensity emitted from a chemical reaction is used to determine the target analyte concentration. Although this particular optical technique can provide simple and fast measurements, it often suffers from notable drawbacks including decreased accuracy due to ambient light noise and inconsistency in the optical detection system. Additionally, dust or insoluble compounds in the sample can easily affect the results.

As an example of electrical detection, chemiresistive sensing has also been used for paper-based analytical devices. This particular technique relies on measureable changes in the conductivity of a sensing material due to the presence of the target analyte. After calibration, the target analyte concentration can be quickly calculated by measuring the change in resistance of the sensing material. This method of detection has been demonstrated for gas detection with functionalized carbon-based electrodes [32–34]. However, because the conductivity of the sensing material can be affected by a variety of chemicals, the sensor selectivity can be negatively affected.

Although each of the above sensing mechanisms have been successfully used by many groups, electrochemical analysis remains one of the most common sensing mechanisms due to its simplicity, quantitative results, high accuracy, high selectivity, and low cost [3,5,12,17–30]. To be clear, chemiresistive sensing and electrochemical detection are both forms of electrical detection that measure current, but they differ in their sensing mechanism. Chemiresistive sensing relies on material conductivity changes that occur due to chemical adsorption or desorption. Electrochemical detection, on the other hand, relies on electron transfer between the electrode materials and the solution. Various electrochemical methods have been utilized for developing paper-based sensors including potentiometry, amperometry, and voltammetry. Generally, potentiometry involves the measurement of voltage between the working and reference electrodes. Sjoberg et al. have reported on a paper-based potentiometric ion sensor. The sensor was fabricated by inkjet-printing gold nanoparticles followed by sintering to improve the conductivity of the electrodes. The working electrode was then modified with a K^+-selective membrane to form an ion selective electrode [35]. Amperometry is another electrochemical sensing method that has gained interest in paper-based sensors. During amperometry measurements, a fixed potential is applied to the working electrode with respect to the reference electrode, and the current resulting from the surface reaction and diffusion of redox molecules is measured with respect to time. Da Costa et al. have reported a fully inkjet-printed electrochemical device on paper using carbon nanotube ink using amperometry to determine dopamine levels [15]. Another paper has reported a working electrode modified with silver nanoparticles as an electrocatalyst and demonstrated a non-enzymatic hydrogen peroxide sensor [17]. Das et al. also used amperometry for hydrogen peroxide detection [36]. Graphene was inkjet-printed to form electrodes, and UV-pulsed laser irradiation was employed to increase the conductivity of the electrodes. Another very common electrochemical sensing technique is voltammetry. This method is an effective electrochemical tool that can provide information about the concentration of an electroactive target analyte. Cyclic voltammetry is widely used to determine analyte concentrations and characterize the kinetic energy of the electron transfer at the surface of the electrode. In this method, the working electrode potential is swept forward and backward, and the current is recorded. Current peaks are observed at the oxidation and reduction potentials. These current peaks are proportional to the concentration of the target analyte.

Ihalainen et al. have employed cyclic voltammetry to characterize their paper-based ultrathin gold film electrodes modified with inkjet-printed conductive polymer [37].

In order to achieve even better selectivity and sensitivity for inkjet-printed paper-based electrochemical sensors, it is also possible to functionalize the electrodes using enzymes. For example, Maattanen et al. modified the electrode surface using glucose oxidase to produce a highly selective glucose biosensor [14]. Alternatively, one group employed electrochemiluminescence as the sensing mechanism to enhance selectivity and sensitivity [50]. This particular method combines electrochemical and chemiluminescence approaches to enhance the sensor's performance. Li et al. achieved dual signal amplification using a graphene oxide-chitosan/gold nanoparticles (GCA) immunosensing platform in conjugation with a functionalized nanoporous silver signal amplification label.

Considering each sensing mechanism, it is quite clear that electrochemical sensing is the most effective method for paper-based sensors. Of course, there are certainly circumstances that require other sensing mechanisms due to specific limitations or constraints, but in the majority of cases, electrochemical sensing provides advantages that far outweigh the disadvantages. Electrochemical detection is very well understood, and there are many resources available for implementing this method properly and interpreting the results correctly. It also provides accurate and selective detection results, enabling the production of high-performance sensors at minimal cost. Table 1 below provides a comprehensive table of paper-based electrochemical sensors for comparison between various approaches. As more and more groups investigate inkjet-printed paper-based sensors, it is likely that the most will focus on electrochemical sensors as the current majority indicates.

Table 1. Summary of previous works on paper-based electrochemical sensors.

Electrode Fabrication Method	Microfluidic Fabrication Method	Ink	Electrode Modification	Target Analyte	LOD [1]	Ref.
Inkjet printing	PDMS [1] casting	Gold	Glucose oxidase	Glucose	0.1 mM	[14]
	Inkjet-printed mineral oil	Carbon nanotubes	-	Dopamine	10 µM	[15]
	Mineral oil casting	Carbon nanotubes	Silver NPs	Hydrogen peroxide	1 µM	[17]
	-	Gold NPs [1]	-	Oxygen	0.0075%	[42]
Screen Printing	Photolithography	Carbon	Sodium dodecyl sulfate	Dopamine	0.37 µM	[21]
	Wax printing	Carbon	Graphene, Polyvinypyrrolidone, Polyaniline, Cholesterol oxidase	Cholesterol	1 µM	[22]
	Wax printing	Carbon	3-HBDH, NAD+ [1]	Beta-hydroxybutyrat	0.3 mM	[23]
	Wax printing	Carbon	-	Lead, Cadmium	1 µg/L	[11]
	Photolithography	Carbon		Gold	5.07 µM	[24]
	Wax printing, Multilayer paper	Carbon	Glucose oxidase, Platinum NPs	Glucose	9.3 µM	[25]
	-	Carbon	Cobalt(II) phthalocyanine	1-butanethiol	0.5 µM	[12]
Screen and inkjet printing	Wax casting	Carbon, polyaniline	-	Ascorbic acid	30 µM	[43]

[1] LOD: Limit of Detection; PDMS: Polydimethylsiloxane; NPs: Nanoparticles; NAD+: Oxidized Nicotinamide Adenine Dinucleotide.

5. Conclusions

Ordinarily, innovation implies production of new materials, creation of new methods, and establishment of new procedures. This is certainly evident with many technological advancements, but it does not truly encompass the meaning of innovation. Innovation requires novelty, of course,

but it would be better to describe innovation in a more general way. In fact, innovation could be simply described as the ability to perform a given task in a new way. Thus, it is not necessarily limited to the use of new materials or new methods. As discussed throughout this review article, the majority of materials, methods, and procedures are not particularly new or novel. Rather, it is the application of these materials and technologies that suggests innovation. The application and need discussed here is that of low cost point-of-care devices for biological and chemical sensing. By focusing on established materials and fabrication techniques, inkjet-printed paper-based electrochemical sensors can be produced with minimal cost allowing for devices that truly meet the needs of patients and the medical community. It is also very likely that these devices will be considered disposable if the cost is low enough.

Throughout this review article, alternatives are discussed—sometimes at length—in order to provide a valid comparison between each of the presented materials and methods. With respect to fabrication methods, inkjet printing and screen printing are indeed the most common methods used today. Each of these methods have been used to fabricate impressive electrochemical devices, but inkjet printing does have a few noteworthy advantages when compared to screen printing. Inkjet printing obviously does not require templates, which saves time and production cost. Additionally, material thickness can be controlled very easily and multiple materials can be deposited simultaneously with inkjet printing.

In terms of materials, conductive nanomaterials were primarily used regardless of fabrication method. Among the reviewed electrochemical sensors, carbon-based materials were the most common. In particular, carbon-based materials included carbon powder, carbon nanotubes, and graphene. Metallic nanowires and nanoparticles were also used in some cases, but it is important to remember that gold and silver—the most commonly used metallic nanomaterials—can significantly drive up the production cost.

All of the devices discussed thus far were tested in various environments to demonstrate the sensing abilities of paper-based electrochemical devices. In some simple cases, basic chemicals were used as the analyte, but in other cases, the authors provided real-world scenarios to establish the validity of these sensors. Potential applications for these sensors include water and air pollution monitoring, cancer screening, and biomarker detection for countless conditions. Traditional laboratories are absolutely required in certain circumstances, but low-cost point-of-care devices are preferred in many cases.

Going forward, there is still much to investigate and many challenges to overcome. For example, inkjet printers can be enhanced to provide better control and greater accuracy during material deposition. The FUJIFILM Dimatix Materials Printer certainly pushes the limits with respect to modern inkjet printing, but its resolution and control is still far inferior to existing semiconductor fabrication processes. Furthermore, most advanced inkjet printing systems are not designed for mass production. As a result, it will be important to continue improving inkjet printing technology in order to produce consistent and reliable sensors on a large scale. With respect to materials, there are many commercially available types of ink from which to select. Although ink diversity is not necessary an issue at this point, it is still very important to choose the right ink to ensure high conductivity electrodes and high-resolution printing. It is also essential to continue investigating various electrode treatments to improve selectivity and sensitivity. Furthermore, paper selection and treatment has also been shown to drastically affect printing. At this point, there is very little literature on paper treatment, but the initial results indicate that paper substrate selection and potential treatment methods may significantly enhance device performance. As further progress is made in the fields of paper-based analytic devices and printed electronics, the production of low-cost point-of-care sensors will not be far behind.

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