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Fabrication and Characterization of Paper-Based Microfluidic Devices

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Abstract: Whitesides group published a research paper about paper-based microfluidic devices in 2007. After that, publication about paper-based microfluidic devices increased very fast. Several advantages of those devices made them better choices than traditional dip stick or lateral-flow assays, including inexpensive, biocompatible, easy-fabrication, small size, eco-friendly, etc. Paper-based microfluidic devices were mainly employed in the field of low-cost onsite detection, such as point-of-care detection for disease diagnosis and environmental measurement. Studies about different fabrication methods were also published during these years, which should be considered before utilization of paper-based microfluidic devices. Meanwhile, some aspects, such as materials and chemicals addition may lead to diverse devices performance, which should be carefully chose during device development. We reviewed fabrication methods and parameters characterization of paper-based microfluidic devices in this paper. Hope those information can give researchers interested in paper-based microfluidics a better comparison.

1. Introduction

Patterned paper-based microfluidic devices were introduced by Whitesides group at 2007 [1], in order to perform an inexpensive onsite detection assay. Those devices were easy-fabrication, biomolecule friendly, pumping-free, inexpensive, and flammable, so the studies about/on them boosted during past ten years. Unlike conventional paper-based platforms, such as dip stick and lateral flow, these devices were fabricated with chemicals (wax, carbon ink, silver ink, polymers) or nanoparticles. Therefore, the reproducibility of those devices were guaranteed, and high-throughput generation of the devices can be realized [2]. Before fabrication, different methods and materials should be considered based on utility. Meanwhile, chemicals can be added in order to endow special characteristics. Therefore, literature about different fabrication methods and characteristics were reviewed in the following paragraph, in order to support information to researchers interested in paper-based microfluidic devices.

2. Fabrication Methods

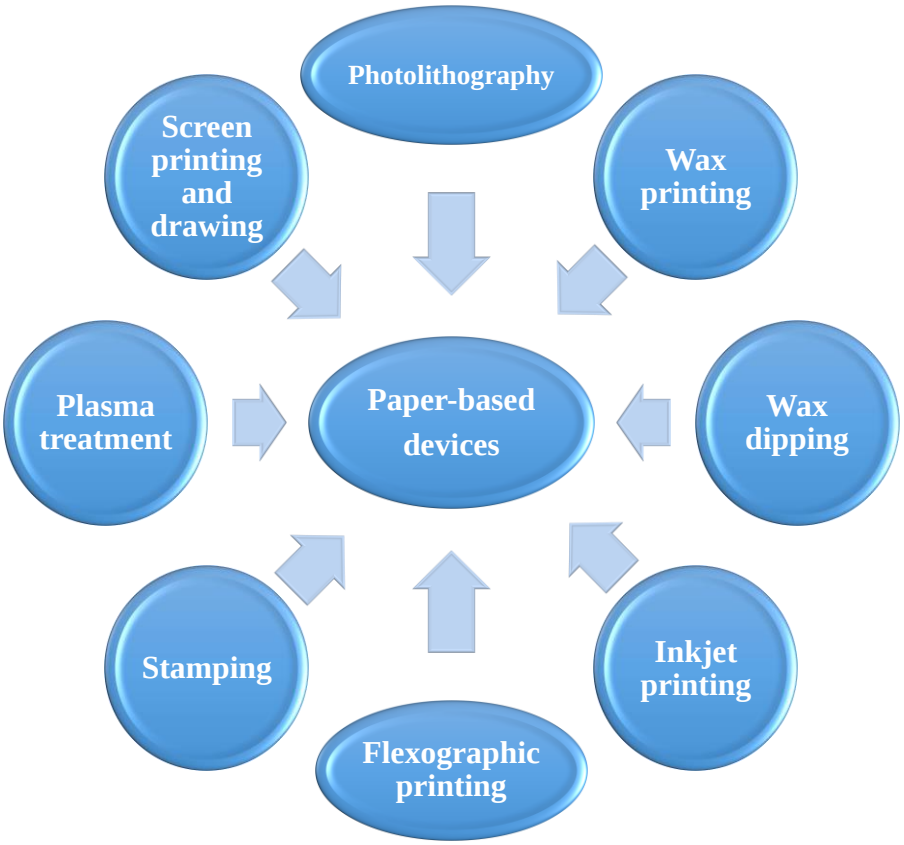

Figure 1: Different fabrication methods of paper-based devices

Table 1: Comparison of different paper patterned methods

Fabrication method	Patterning material	Fabrication Tool(s)	Possible for high throughput paper patterning?
Photolithography	Photoresist (SU-8, PDMS, etc.)	Computer, hotplate, UV lamp	Yes
Wax printing	Wax	Solid-ink printer	Yes
Wax dipping	Wax	Mould and permanent magnet	No
Flexographic printing	Polystyrene	Flexography rolls	Yes
Screen printing	Ink	Mould	No
Plasma treatment	Plasma	Vacuum plasma reactor	Yes
Laser treatment	CO_2	Laser cutting and engraving system	Yes
Pen drawing	Ink	Mould or ruler	No
Inkjet printing	Organic solvent and sensing chemicals	Inkjet printer	Yes
Stamping	Chemicals	Mould	No
Deposition	Metal	Mould	Yes

In paper fabrication, a hydrophobic area is generated by either of two processes: coating then

etching paper pre-treated with hydrophobic material; or dissolving hydrophobic materials that are pre-coated onto paper. The first process uses procedures such as photolithography, wax printing, wax dipping, and flexographic printing, while the second process uses methods such as plasma printing and laser printing (Figure 1). Inkjet printing is a specific method that could be used to generate either hydrophobic or hydrophilic areas, depending upon the material printed. Deposition and stamping of an assembled metal or chemical precipitate onto paper can be performed. The desired material can also be drawn onto the surface of the paper with a pen to create a hydrophobic barrier and a conductive line. The reviewed fabrication methods were compared in Table 1.

2.1. Photolithography

In 2007, the Whitesides group introduced a new method for fabricating paper as an analytical detection platform and began a revolution in paper microfluidic devices [1]. They employed photoresist polymer SU-8 to form a hydrophobic barrier on Whatman No.1 chromatography paper (1 Chr) under UV light. The pattern was designed with a computer, and printed as a mask. By utilizing this method, a μPAD with 184±12 μm channels could be generated with only a 200 μm mask, computer, oven, and UV-lap [1, 3]. They detected glucose and BSA in 5 μL of artificial urine solution simultaneously with this device using a 1.5 cm x 1.5 cm microfluidic setup after loading the sample for 10 min [1]. The method provided a solution for low-cost on-site detection. The group also experimented with utilizing octadecyltrichlorosilane (OTS) to generate the hydrophobic barrier instead of SU-8, because it is less expensive, and does not require a special clean room [4]. The minimum widths of the hydrophobic and hydrophilic channels fabricated with this method were 80 μm and 130 μm.

In later publications, the Whitesides group further simplified this method, and reported on the so-called “Fast Lithographic Activation of Sheets (FLASH)” technique [3]. They placed a piece of filter paper between an adhesive transparent film and black paper, and printed the desired pattern as a mask on the film with an inkjet printer. After exposing the mask to a UV lamp, the film and black paper were removed, leaving only the filter paper with the desired pattern. They patterned paper into millimeter-sized channels, and could fabricate several setups in one sheet of letter-size paper within 30 min. The Whitesides group also tested this method with different formats, such as 96 and 384- well microtiter plates, which were named microzone plates [2].

2.2. Wax Printing

In wax printing, the designed pattern is printed onto 1 Chr paper with a solid-ink printer [5]. The hydrophobic barrier was generated with melted wax which was baked in an oven after printing. The baking step caused the wax to penetrate the paper in the z-dimension and extended the hydrophobic barrier along x- and y-dimensions. The smallest hydrophobic barrier obtained was 850±50 μm which was a result of a 300 μm printed line [5]. Compared to the photolithographic approach, the channels obtained were much large compared and the boundary of the hydrophobic and hydrophilic regions were more coarse [5]. Thus, the wax printing method is harder to control compared to photolithography. Additionally, the paper-based microfluidic setup was tested with total protein, cholesterol and glucose detection in biological fluids.

2.3. Wax Dipping

In The Laiwattanapaisal group developed a wax-dipping method to fabricate cellulose paper by holding a piece of paper between a patterned mould, fixed with a permanent magnet, and a glass slide [6]. Then, the setup was dipped into melted wax for 1 s at 120-130 ℃, and a hydrophobic

layer was formed. The thinnest channel printed with this method was 639 ±7 μm. They tested the microfluidic setup with BSA and glucose detection simultaneously.

2.4. Inkjet Printing

The hydrophobic barrier generated with inkjet printing has been utilized by several research groups. However, the Citterio group utilized inkjet printing to generate a hydrophilic area on a pre-treated hydrophobic paper surface with an inkjet printer [7]. The filter paper was submerged in polystyrene dissolved in toluene to create a hydrophobic area. The hydrophilic channels and sensing area were generated by 10 cycles of printing toluene onto the hydrophobic paper. Based on the detection target, the corresponding chemicals were printed onto the sensing area. They tested the microfluidic setup simultaneously detecting protein, glucose and pH in a 4.5 μL sample after a 10-min incubation. The average width of the flow channels was 450 to 470 μm with this method. The channels generated with this method were larger and less precise than photolithography method, because the hydrophilic area was generated by dissolving polystyrene in toluene.

2.5. Flexographic Printing

The Erho group developed a flexographic printing method for paper-based microfluidic fabrication [8]. They utilized roll-to-roll flexography units to print polystyrene onto chromatography paper. This method could generate channels as small as 500±30 μm. The printed channel was larger than the designed pattern due to the liquid ink expansion. They tested glucose with a patterned paper setup in 20 μL sample after 10-min incubation. Different concentration of glucose can be seen with bare eyes as a gradual color change from pink to yellow.

2.6. Stamping

The stamping method which was introduced by the Whitesides group demonstrated the patterning of insoluble salts and metals on paper, as precipitates from chemical reactions [9]. In this technique, the template was printed with a laser printer or by a wax printing method, and one reagent was added onto the hydrophilic area. The template was then stamped onto paper that had been covered with the other reagent to deposit the precipitate in a pattern corresponding to the printed template.

2.7. Plasma Treatment

The Shen group developed a paper-based microfluidic setup using a plasma treatment method [10]. The hydrophilic area was formed on alkyl ketene dimer treated hydrophobic filter paper by a metal mask with a vacuum plasma reactor. This method takes longer time to treat the paper (>45min). Also, a vacuum plasma reactor and a metal mask are required, which cost more than the methods listed above.

2.8. Screen Printing and Drawing

Screen printing is the most straight forward way to generate a hydrophobic area on pape r[11-15]. A method developed by the Li group involved drawing a hydrophobic barrier onto a paper surface with a permanent marker using a metal template [16]. They tested the patterned paper with prostate-specific antigen detection. With a pen, researchers also drew graphene on paper [17]. They also loaded graphene on a PTFE membrane with a graphene ink cartridge. By drawing on the back of the

graphene paper, a graphene conductive line is formed on paper below the graphene paper by force. They characterized conductivity by folding the resulting paper, and made a circuit out of it.

The Ziaie group has fabricated paper with a laser treatment method [18]. They applied CO_2 laser on pre-treated paper with a computer-controlled laser cutting and engraving system. They obtained a 60 μm wide line with this method.

3. Characterization

The fabricated paper was characterized by several groups from different aspects. Different paper materials and patterning materials are both tested for several patterning methods. Meanwhile, the flow rate at the hydrophilic channel was tested with/without external forces. Furthermore, the electrochemical characteristics were tested with different paper materials, and the reproducibility was checked after folding.

3.1. Different Paper Materials

Different paper materials were tested with a photolighography method, including coffee filters, Kimwipes™, and laboratory wipes from TechniCloth® [2]. The results showed that the capacity (volume) of each well depended on the thickness of the paper.

Besides using 1 Chr paper, the Whitesides group tested TechniCloth wipes and printer paper with wax printing method as well. The 1 Chr paper is pure and homogeneous, which resulted in a more reproducible microfluidic setup [5].

The Ziaie group tested parchment paper (silicon coating), wax paper, and palette paper (plastic coating) with a laser-treatment method [18]. They achieved good resolution (60 μm wide line with 80 μm hydrophobic separation) on parchment paper. The printed parchment paper did not have any difference in surface properties after three-week storage.

The Whitesides group also tested the electrochemical properties with different paper materials [19]. This will be introduced in detail in section 3.4.

The Kadir used hydrophilic cotton cloth instead of paper, as the material for microfluidic setups [20]. In order to fabricate the cloth with a specific pattern, they utilized a paper mold pre-dipped into wax. By heating the pre-treated paper on the top of cloth, the wax melted and transferred to the cloth, forming a hydrophobic barrier on the cloth. With this method, they fabricated 1 mm wide channels for solution delivery.

3.2. Different patterning materials

The Whitesides group compared SU-8, SC (a cyclized poly (isoprene) derivative)[2], and poly(dimethylsiloxane) (PDMS)[21]. As an elastomer, PDMS is more flexible than other photoresists, so it can fold easily without causing damage.

The Ihalainen group characterized the physical properties and electrical performance of metal or polymer fabricated papers [22]. They found the small printed line width was obtained with less polar ink that has high surface tension. However, the wires printed on plastic material have better electrical performance than that printed on paper.

3.3. Flow rate

Several studies have been performed to characterize the liquid flow on cellulose paper by capillary force [23, 24]. The Yager group visualized the liquid flow on a wick using two methods: caged fluorophore marking and electrochemical marking [23]. Under only the capillary force, the

flow distance showed a linear relationship with time measuring by both the testing methods. They were also interested in the flow rate with uniform width, and sudden-expansion and -contraction strips, and derived a formula for the flow time [24]. They found the sudden-expansion would slow the diffusion on one direction. On contrary, the sudden-contraction increased the wicking distance.

Two studies have characterized liquid flow in presence of external forces [25, 26]. The Yeo group compared the flow under capillary force and with the aid of surface acoustic wave (SAW) [25]. Under specific output from SAW, the flow rate is accelerated and unified, and the mixture of two flows was uniform and reproducible. A theoretical model was generated by the Cho group for the flow distance upon capillary driven competes with different centrifugal force [26]. The higher speed and longer time, which increased the centrifugal force, resulted in shorter wicking distance.

3.4. Electrochemistry characteristics

Choosing the appropriate paper material is very important for electrochemistry because the different surface resistivity. The Whitesides group compared different paper materials patterned using deposition and showed a correlation between surface resistivity and surface roughness [19].

In the same paper, the group experimented with spraying metal onto a paper surface and mounting small electric devices onto it through conductive brackets [19]. With this deposition method, they have made a circuit on the paper which they could fold into a desired shape.

As previously mentioned, the Ihalainen group concluded that better electrical performance was achieved for the wires printed on plastic material than the ones one paper [22]. Also, they discovered that different printing patterns could change the electrical properties of printed wire. The resistance would increase if the printed line were long and narrow, which is due to the higher surface roughness [22].

4. Conclusions

Paper-based microfluidic devices were initiated with easy and fast patterning methods, such as wax-printing and photolithography. Because of the characteristics of paper, which include its low cost, easy fabrication, and disposable, it is an ideal material for point-of-care detection. An abundance of recent studies reported different fabrication methods, in order to create a cheaper, easier fabrication method with high reproducibility. Meanwhile, publication about surface modification and characteristics of paper-based microfluidic devices are also reviewed, which should be considered during device design. This paper can give a better information for researchers interested in paper-based microfluidic devices.

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