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Comparative study on obtaining paper and thread-based microfluidics via simple fabrication techniques

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Abstract

Microfluidic paper-based analytical devices (µPADs) and microfluidic thread-based analytical devices (µTADs) have recently been introduced as a new class of on-site monitoring devices. Creating hydrophilic channels with hydrophobic barriers on papers/threads produces µPADs/µTADs. Fabrication is a crucial step in creating durable µPADs/µTADs that can withstand various liquids and impact the device's performance. Fabrication materials with distinct physicochemical properties allow microfluidic systems with sophisticated functions to be customized for specific applications. We present flexible and low-cost fabrication methods for µPAD and µTAD platforms. Platform designs and fabrications were implemented using a trial-and-error method for various designs with varying parameters. All production methods presented in the method section were used in µPAD production. For comparison studies, only the dipping method was used in µTAD production due to its ease of application. In this study, we tried to reveal the strengths and weaknesses of the production techniques and the resulting microfluidic platforms. A leaching test was performed with water solutions containing red ink. The compatibility of the hydrophobic walls of the platforms was tested with several solvents (isopropanol, methanol, and acetone), deionized (DI) water, and phosphate buffer solution PBS and compared. Patterning paper with polydimethylsiloxane (PDMS), white glue, alkyl ketene dimer (AKD), beeswax, and paraffin are much more flexible and simpler than traditional photoresist-based fabrications. The advantages and disadvantages of fabrication techniques; solvent resistance and wicking behaviors of platforms were discussed in the last part. The fabricated microfluidic platforms can be functionalized and used in many areas where analytical tests are applied. Studies on diversifying channel geometries and increasing resolution need to be continued. It should be investigated which devices can be used to obtain qualitative and quantitative results. To make simple and cheap production techniques suitable for mass production, studies should be carried out from different branches.

1. Introduction

Recent advances in material science have resulted in the convergence of numerous sciences and technological fields, including engineering, chemistry, physics, biology, and medicine. Microanalysis systems have further transformed these fields [1]. The reduction to the microchannel scale not only miniaturizes and integrates the analytical device but also exerts many micro and nano effects on the fluid, endowing microfluidic chips with greatly improved performance compared to that of a traditional analysis system [2]. At the microscale, various forces exert a greater influence compared to those encountered in everyday life. The effects that gain prominence in microfluidics encompass laminar flow, diffusion, fluidic resistance, surface area to volume ratio, and surface tension [3]. Microfluidics was defined as the integration of basic operating units such as sample preparation, biological and chemical reactions, separation, and detection to complete various biological or chemical reaction processes and analyze their products [4] allowing for precise control of micro-nano

liquids [5]. Scientists have proposed microfluidic systems as a method for developing new tools [6] for various fields [7]. Microfluidics offers many advantages over traditional systems [8] due to the benefits of high sensitivity, rapid detection, compact size, low reagent consumption, and wastage, low cost, [7] assay automation, enriched detection performance, user-friendliness [9] faster processing times, and improved analytical performance [8].

The evolution of microscale devices from closed to open device embodiments, including open microfluidic capillary systems [10]. Among microfluidics, self-driven microfluidics typically employs surface hydrophilic properties or capillary forces for fluid transport and handling. It is distinguished by its self-driven nature, and the absence of an additional pumping and energy source [11]. Paper-based microfluidics are devices made of paper or other porous membranes that use capillary action to manipulate small (10^{-6} to 10^{-9} L) volumes of fluids [12]. Low Reynolds numbers (Re) in microfluidic devices ($10^{-3} > Re > 10^{-5}$) result in laminar flow, which allows effective control of critical reaction parameter such as temperature, mixing velocity, and reagent concentration [13].

µPADs first described by Whitesides' group [14], are sustainable alternatives to traditional polymer or glass-based microfluidic devices [15]. In comparison to regular microfluidic devices, µPADs have flexibility, hydrophilicity, lightweight, and biocompatibility, and can be operated without pump power to transport fluids of small size [16]. µPADs have recently been introduced as a new class of on-site monitoring devices specifically for use in developing countries [17]. To carry out the desired physical, chemical, and biological processing, multiple components, such as reaction vessels, mixing structures, or separation chambers, can be patterned in an integrated manner onto a piece of paper [18]. Since their introduction, they've been widely used in a variety of fields, including food safety, cell culture, and point-of-care (POC) applications [19].

Since its invention, paper has played an important role in everything from writing scriptures to modern-day chemistry [20]. Paper was first introduced as a potential material for microfluidics in 1949 [21] when a heated dye was used to impregnate a filter paper with a wax barrier, the goal was to create a restricted flowing channel to reduce the amount of sample used [22]. The paper was widely used due to its unique fiber structure, porosity, capillary force drive, absorbency, air permeability [23,24], and sustainability [25]. The biological function of cellulose, as well as its numerous applications, are based on its distinct fiber morphology. Elementary fibrils, microfibrils, and microfibrillar bands define the morphological hierarchy [26]. Paper's porosity is caused by spaces between the fibers, uncollapsed fiber lumens, and the inherent porosity of the fiber walls [27]. Paper surface modification is typically accomplished by fabricating µPADs through chemical modification, physical deposition, or physical blocking of its pores to tune the paper material to have the desired properties for direct use in critical experiments/applications [28]. These agents alter the paper's liquid-wetting properties, allowing the formation of hydrophilic-hydrophobic patterns [29]. Creating hydrophilic channels with hydrophobic barriers on papers results in µPADs [30]. The two parallel hydrophobic lines function as channels because the hydrophilic sample solution cannot penetrate the hydrophobic line or barrier, causing the liquid to flow in the channels due to capillary action [31] also known as wicking in contrast to traditional silicone-based microfluidic chips [32]. Capillary action is caused by intermolecular forces between the solution and the surrounding porous material surfaces and is unaffected by gravity, inertia, or any other external forces [33].

There are two fundamental ideas for creating open channels: the first is to confine liquid by designing a solid structure, such as grooves, suspended microfluidics, and hanging droplets. The second step is to modify the substrate to be hydrophilic/hydrophobic, and then confine the aqueous samples at the hydrophilic pattern [34]. A µPAD device consists of a detection zone, a sample zone, and a flowing channel that transports the sample solution from the sample zone to the detection zone [35]. The most common techniques for defining barriers and zones are cutting, printing, drawing, dip-coating, plotting, and photolithography (Figure 1) [36]. While most reports used photolithography to create barriers, newer, simpler, faster, and less expensive technologies have emerged, enabling implementation in research groups with limited resources [37]. Recent advancements in fabrication methods have concentrated on reducing fabrication time, cost, and complexity, increasing spatial resolution, and shrinking device sizes [38]. Fabrication is a critical step in the development of effective µPADs that are resistant to a variety of liquids [39] and strongly influence the final device's performance [40]. Fabrication materials with distinct physicochemical properties enable microfluidic systems with sophisticated functions to be tailored to specific applications [41].

Aside from paper, threads of cotton, nylon, silk, polyester, or other fibers have been proposed as substrates for microfluidic diagnostic systems, also known as µTADs [42]. They are more flexible and wearable alternatives [43] with higher mechanical strengths under wet conditions [19]. In addition to similar advantages provided by paper threads have varying wicking and adsorptive properties to meet the needs of various research needs [44].

Threads have stretchability, high mechanical strength, and durability, making them an ideal substrate for the development of wearable analytical devices [46].

Detailed studies must be done about substrate properties, wicking rate, material durability, and fabrication methods. Here we present flexible and low-cost fabrication methods to obtain µPAD and µTAD platforms. All production methods presented in the method section were used in µPAD production. For comparison studies, only the dipping method was used in µTAD production due to its ease of application. The advantages and disadvantages of fabrication techniques; solvent resistance and wicking behaviors of platforms were discussed and summarized in the last part.

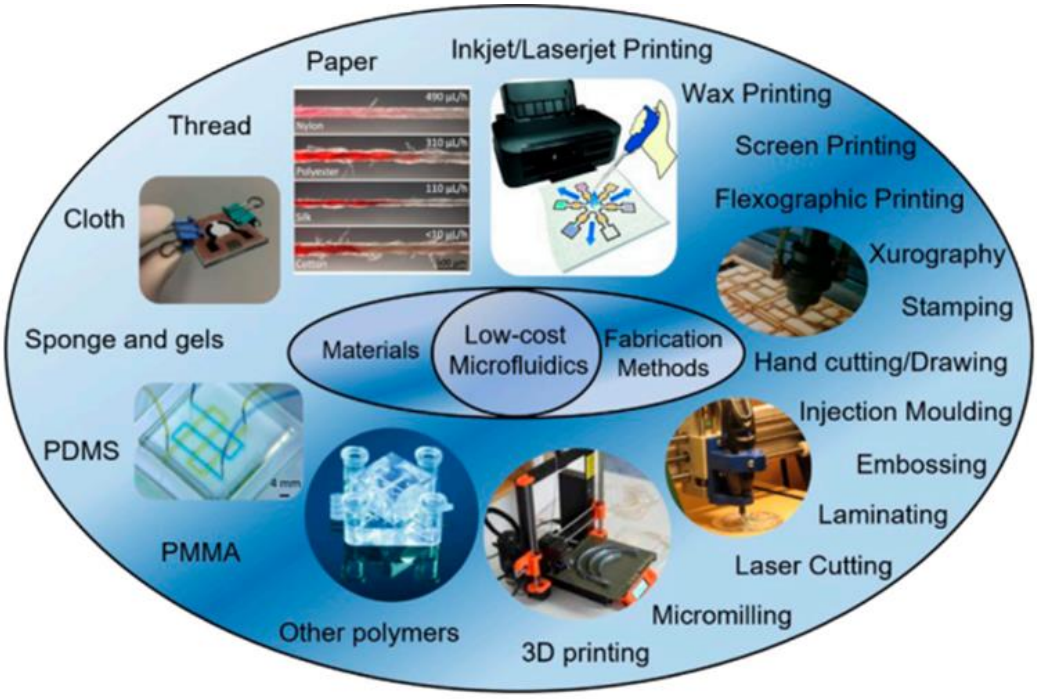

Figure 1. Microfluidic fabrication materials and techniques [45].

2. Materials and method

2.1. Materials

Coarse filter paper (ISOLAB); hexane, n-heptane, methanol, isopropanol, and acetone (MERCK); PBS (Sigma-Aldrich), were purchased from AS Kimya Ltd. PDMS and, PDMS curing agent (SYLGARD™ 184 Silicone Elastomer, DOW Corning) were purchased from C3 Teknoloji Ltd. White glue, paraffin, beeswax, pens, and magnets were purchased from local markets. AKD (Diper Chemical Company) was taken from the forest engineering department of Istanbul University. Evolon® (Freudenberg) was taken from the textile engineering department of Istanbul Technical University.

2.2. Fabrication methods

The filter paper was used for all µPAD platform fabrications. Platform designs and fabrications were implemented using a trial-and-error method for various designs with varying parameters. Evolon® fabric was also used for the dipping method to obtain the µTAD platform.

2.2.1. Creating channels and test zones with PDMS and white glue

In the first approach, hydrophilic channels or zones of interest are defined by drawing with hydrophobic inks. Commercial ballpoint pens were used to draw hydrophobic barriers on the filter papers. The tubes of pens were emptied and replaced with the prepared PDMS and white glue solutions. Various solutions were prepared with hexane during PDMS studies. PDMS was first used by dissolving it alone in hexane at ratios of 2:1 and 3:1. Solutions at the same ratio were also prepared after mixing PDMS and curing agent at a ratio of 10:1. After patterning, paper samples were kept at 70 °C for 1 h in an oven [47].

Another material used in the drawing technique is white glue. This substance is an emulsion of poly (vinyl acetate) (PVAc) in an aqueous solution. It was used undiluted and in 50% (v/v) dilution form. Drawings were made on single and double sides of the filter paper and the results were compared. Glue-patterned samples were kept at 130 °C for 1 h in an oven to obtain an insoluble structure. The glue-coated papers were then exposed to UV/Vis light (SUSS MicroTec Mask Aligner) at 800 W lamp power and 55-56 mW/cm^2 light intensity (30 min) for cross-linking to increase chemical resistance [37].

2.2.2. Creating channels and test zones with AKD

Patterns were created on a computer using the CATIA V5R21 software, then transferred to a printer and printed on filter papers. The printer was modified by replacing the ink cartridge with the AKD-heptane solution at ratios of 0.6, 2, and 4% (w/v). Printer cartridges were filled with AKD solutions and the designed channels were printed on A4-size filter papers. After evaporation of heptane paper samples were heated in an oven at 100 °C for 45 min to cure the AKD [48].

Another technique suitable for AKD is plasma treatment. The filter papers were hydrophobized using AKD-heptane solutions at the ratio of 0.6, 2, 4, 10 % (w/v). After evaporation of heptane, paper samples were heated in an oven at 100 °C for 45 min to cure the AKD and then placed into a vacuum O_2 plasma reactor (HARRICK PLASMA-Plasma Cleaner- USA). Heavy metallic masks were used to create test zone geometries. O_2 was set at 5 bar and taken into the plasma cabin for 3 minutes. Plasma was applied for 10 min at a high plasma level of the device (18W) [49].

2.2.3. Creating test zones with paraffin and beeswax

For the dipping method, paraffin and beeswax pellets were placed in a beaker and heated (75 °C) on a hotplate (IKA C-MAG HS7) until melted. Filter papers were cut into pieces, and round magnets were placed on both sides of the papers to hold them together temporarily. The assembly was then immersed for 1 second in a chamber of melted wax. Magnets were peeled off the paper after it had cooled to room temperature [50]. Since the dipping method can be easily applied to the threads, hydrophilic areas were created on the Evolon® for comparison purposes.

2.3. Evaluating the solvent compatibility of the hydrophobic walls

Various channel and test zone models have been designed and fabricated using various techniques to determine the suitable geometries. A leaching test was performed with water solutions containing red ink. The compatibility of the hydrophobic walls was tested with several solvents (isopropanol, methanol, and acetone), DI water, and PBS and compared. To observe leakage and understand the minimum volume required to fill the channels and test zones 5, 10, 20, 40, 60, 80, and 100 µL solvents were loaded on test zones and one end of the channels. In comparison studies with thread-based platforms, 200, 300, and 400 µL were also tested.

3. Results

Patterning is the first step to fabricate any paper or thread-based device [51]. Non-covalent cellulose treatment is based on filling the void spaces with a hydrophobic material (solid melt or polymer solution), creating a barrier to aqueous liquids [52].

The methods can be further divided into additive and subtractive methods [53], additive methods selectively hydrophobized only the barriers, while subtractive methods hydrophobized the entire paper before selectively restoring hydrophilicity to the channels [54]. The drawing, printing, and dipping methods used in this study can be shown as examples of additive methods. Plasma treatment is a subtractive method.

Photolithography, the first reported fabrication method, is known for its high resolution [55] but is laborious, time-consuming, has a high cost per device; and necessitates sophisticated instrumentation housed in expensive cleanrooms [56]. Alternative and more efficient methods and substrates are required for paper and thread-based microfluidics to achieve its true purpose. In this study, we proceeded with simple non-covalent patterning techniques. The first stage of the study is the production of various channels and the second stage is the test of the solvent resistance of these channels.

3.1. Drawing with PDMS and white glue

In addition to traditional fabrication methods, pen-on-paper (PoP) strategies, which are based on directly writing functional materials on paper with various pens, have emerged as simple and alternative approaches to creating hydrophobic barriers on paper substrates [57]. The first part of the study focuses on the fabrication of hand-drawn test zones (Figure 2). For comparison, two different materials, PDMS and scholar glue, were used in varying ratios. Enough pressure and weight, along with the pen nib, allow polymers to fully penetrate the filter paper. The solvent evaporates almost immediately, leaving the polymers on the paper to form the channels' hydrophobic walls. When we use PDMS alone, it does not plasticize and remains as a gel. Mixing with hexane improves the paper's absorption. As the hexane ratio increases, so does the ability to absorb; however, spread occurs. The addition of a curing agent improves plasticization, but because it dries faster, it may interfere with the paper's absorption. The mixture with the curing agent becomes unusable the following day; only PDMS can be used for a few days.

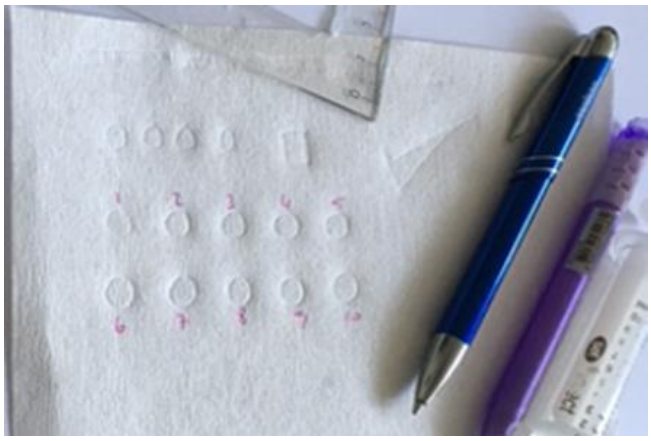

Figure 2. PDMS patterned filter paper.

Advantages of PDMS include its transparency, ease of availability, nontoxicity, odorlessness, and ease of dilution in hexanes or other organic solvents [58]. However, it required special preparation of PDMS diluted in hexanes and an extra heating step for polymerization after deposition. Because of its low solid-vapor interfacial free energy (21 erg/cm^2), PDMS can wet the entire depth of the paper. Solutions with higher viscosity (i.e., with greater than 80% PDMS (w/w) did not penetrate the paper; solutions with less than 67% PDMS (w/w) led to irregular lines [47]. The ink viscosity and tip pressure must be optimized to ensure that the hydrophobic ink penetrates the thickness of a piece of paper [59].

Another material used in the drawing method is white glue, which is cheaper and has a more viscous structure than PDMS. This PVAc-based glue was used both in nominative and in aqueous solution (50% (v/v) form. Although it is soluble in water, it becomes insoluble after baking at 130 °C. Exposing the UV light cross-linked the polymer and increased chemical resistance. Glue is attractive because it is inexpensive, globally available, non-toxic, and most importantly, does not require organic solvents [37]. Glue is percolated on both sides of the paper, which is required for the creation of a leak-proof device. To fabricate solvent and surfactant-

resistant structures, an additional heating step for polymerization and UV treatment is required.

PDMS drawings require the use of an organic solvent (hexane), which can damage the original structure of the filter paper [60]. While for white glue there is no such a problem. To take this technique to further levels, drawings were made with devices such as plotters and 3D pens.

Walia et al. [61] demonstrated a pen-plotter as a fast-writing tool filled with an inexpensive, aqueous phase ink composed of bovine serum albumin (BSA). Different concentrations such as 15-20-30% were tried and it was concluded that 20% concentration viscosity was suitable for printing BSA with a plotter. The proper viscosity of the used ink material helps block the paper pores effectively and form a good hydrophobic barrier. Nuchtavorn and Macka [62] present a novel, highly flexible, and low-cost fabrication method based on a desktop digital craft plotter. The method can print two or more water-resistant inks quickly, in a variety of designs, and without alignment issues. No additional heating stages are required when using this type of ink. Sousa et al. [63] described for the first time the use of a 3D pen to pattern papers with acrylonitrile butadiene styrene (ABS).

Using a ballpoint pen to define the test zones reduces the number of reagents used and waste, making it green engineering. This technique is inexpensive, but the pattern resolution is limited [59]. Also, it is almost impossible to produce devices on an upgraded scale and at a high speed [48].

3.2. Patterning with AKD

Inkjet technology has evolved into a versatile tool for a variety of industrial fabrication processes [64]. In its most basic form, an inkjet printer dispenses picoliter-sized droplets of liquid (ink) onto a substrate at a user-defined position [52]. In this study, PDMS and white glue were also used in the printing process to produce high-resolution patterned papers, but they clogged the inkjet printer cartridges. Therefore, patterning was continued with AKD. AKD was used as a solution in heptane at the ratios of 0.6, 2, and 4% (w/v). Since AKD is colorless, coloring studies were carried out with pigment-based paints to reveal the patterns on the paper. Unfortunately, these particle-based colorings resulted in nozzle clogging.

Examples of microfluidic devices with one, two, or four detection zones have been successfully developed (Figure 3) with 2 and 4% AKD solutions. However, due to the AKD spread of 0.6 %, it is difficult to produce the exactly designed patterns with high resolution. Thickness uniformity results can be influenced by the polymer ink's physical properties and interaction with the substrate [65]. Fluid properties must be within an acceptable range to dispense fluids other than consumer-grade commercial inks. Typically, the permitted range of physical properties is as follows: The viscosity η (1-25 cP), surface tension σ (20-50 dyne/cm), ink density ρ (0.9-1.1 g mL^{-1}), and particle size should be less than 1 μm [66].

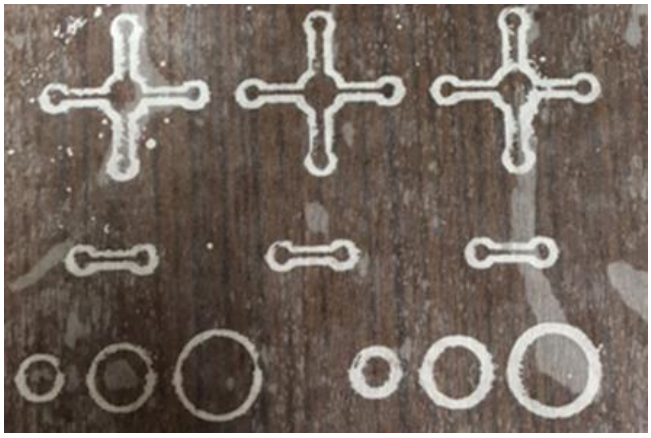

Figure 3. AKD printed filter paper.

AKD needs to be bonded to the paper with hydrogen bonds by keeping it in the oven at 100 °C for 5 min. So, it can finish penetrating throughout the paper and form a hydrophobic barrier while not moving sideways enough to block the channel [67].

Instead of AKD, chemical sensing ink formulations can be printed on different types of [63]. The laser printer's toner can be directly printed over a paper matrix and re-flow with heat to create a hydrophobic barrier within the paper thickness [68]. Wax-based materials can be deposited on chromatography papers via specific wax printers [69].

Inkjet printing's non-contact nature enables the deposition of inks on a variety of substrates, including papers, fabrics, polymers, metals, and biomaterials [70]. It is a non-contact and maskless approach with reduced material waste, low cost, and scalability for large-area manufacturing. Due to these characteristics, it is an appropriate technique for combinatorial studies [71]. Polymers such as PDMS and AKD are non-biodegradable, necessitate organic solvents, and pose risks to human health during their life cycle. Approaches like screen-printing for μPAD fabrication from simple biodegradable polymer Polycaprolactone (PCL) can solve this kind of problem [72].

Plasma treatment is among the chemical methods that change the surface properties of paper. After the paper is coated with a suitable hydrophobic material, the whole surface is made hydrophilic again by plasma treatment [73]. In our experiment, following plasma treatment, the AKD-covered regions at all tested ratios could be rendered hydrophilic. The desired test zones could not be created with the applied metallic masks. Due to excessive plasma etching, the paper samples returned to their fully hydrophilic form. According to the studies conducted, hydrophilic areas could be created in designed shapes using materials that adhere strongly to each other from both sides of the paper, such as magnets.

3.3. Dipping method in paraffin and beeswax melts

The paper is clipped in the center of the round magnets and dipped in melted paraffin or beeswax. After cooling and solidification, hydrophobic barriers are formed due to the penetration around the magnets (Figure 4). The final size of the hydrophilic channel is

determined by the size of the round magnet used. We designed 8-9 mm circles via this technique which serve as barriers. Many biochemical detection methods, such as ELISA, require arrays of hydrophilic dots or microzone plates [74]. The test zones produced can be used in this kind of detection method.

Figure 4. Beeswax patterned filter paper.

The advantages of this method include low reagent costs and a simple procedure. However, due to poor reproducibility and the need for metal molds of a specific shape that are not readily available, mass production is not feasible [75]. It is a more efficient and cost-effective patterning method compared to other tried techniques. It only requires wax dipping, and the test zone was created in less than a minute with subsequent soaking and standard heating techniques. One disadvantage of materials like AKD, paraffin, and beeswax is that they require high temperatures to work with. Another limitation of magnet-based methods is that the resulting test zone shapes are determined by the shape of the magnet. This limits the ability to create the desired designs.

3.4. Evaluating the compatibility of the hydrophobic walls

The type of paper used is entirely determined by the user's application, but it can and will have a significant and predictable impact on performance and fluidic transport [76]. Filter papers were used in all mPAD platform productions. This kind of cellulose chromatography paper had an accessible specific surface area of 9.76 m^2/g [77].

In paper device fabrication, the resolution is typically reported in terms of the minimum functional channel and barrier widths, in this case, meaning that channels wick fluid and barriers do not leak [54]. The next step in our study is to observe the resistance of hydrophobic channels to water, PBS, and organic solvents. All channels and test zones were able to keep the red dye solution within their barriers. Cellulose is insoluble in water and most organic solvents due to its supramolecular structure [26]. Therefore, the determining factor of the study is the behavior of alcohols and acetone within the channels and test areas.

When PDMS is used in its pure form during the drawing process, it cannot create a complete barrier, so leaks occur. When used with a curing agent, we could create hydrophobic channels and test zones that are suitable for water and PBS. It has been observed that water can move through the capillary effect in all channels obtained with PDMS+curing agent, white glue, and AKD. Capillary flow is the natural wicking of liquids in small spaces without the aid of external forces [78]. When the energy reduction associated with the larger liquid-solid surface area outweighs the energy increase associated with the larger liquid-air interface area, the fluid front advances in the channel [79]. However, some real samples may contain solvents or reagents that can break the integrity of the hydrophobic barrier [52]. Areas created with PDMS could not be used with solvents such as alcohol and acetone. These solvents crossed the channel walls and found dispersed to other parts of the chromatography papers. In areas obtained through AKD, alcohol, and acetone behaved similarly. When the fluid fills the entire microchannel, it forms a meniscus at the end. This meniscus is the same size as the liquid head meniscus, but it faces the opposite direction. These opposing capillary forces keep the solution within the microchannel [80]. In a study, leakage has been observed in printed channels when using solvents that have a surface tension lower than 30m Nm^{-1} [81]. The motion of the liquid-solid contact line is dominated by viscous and surface tension forces rather than inertial and gravitational forces [82]. When the surface tension of a liquid is lower than a certain value (Table 1), the liquid tries to move not only in the hydrophilic channels but also in some regions of the barriers that remain hydrophilic. While materials such as AKD and wax hydrophobize the paper, they also reduce the surface energy [29].

Table 1. Surface tensions of the liquids used in the study [83].

Solvent	Surface tension (mN/m)
Isopropanol	23.00
Methanol	22.70
Acetone	25.20
Water	72.80
PBS	69.50*

When white glue is drawn on one side of the paper, the resulting channels leak; however, when drawn on both sides of the paper, no leakage occurs. While the white glue used in the drawing technique is normally a water-soluble material, it becomes insoluble after baking and UV cross-linking processes and acts as a hydrophobic barrier. Because the glue has higher walls than PDMS, alcohols and acetone can flow through the channel. In a study, it was observed that the channels produced from resin using a 3D pen were resistant to organic solvents other than ethanol [63]. It was found that once formed, the glue barriers demonstrated high resistance to aggressive solutions such as surfactants, organic solvents, and strong acids and bases [37]. Studies have shown that the reason why solvents with low surface tension such as alcohol and acetone cannot penetrate paraffin and wax walls is that the channel walls are high due to the production technique. Paraffin and beeswax strengthened the resistance of microchannel barriers to organic solvents, preventing leakage. In a study laser ablation method allowed for the fabrication of parafilm barriers resistant to various organic solvents [39]. Microscale detection is a distinguishing feature of the microfluidic technique. As a result, optimizing the volume used is a necessary step [35]. Since the resolution was low in the hand-drawn channels/test zones, the maximum liquid volume that could be used in the

channel could not be determined. However, in studies conducted with AKD printing, it was observed that a minimum of 5 and a maximum of 20 µL of liquid loading was required to ensure capillary flow in the channels. Capillary-driven microflows differ from pressure- or flow-rate-driven ones in that the engine of motion is located at the liquid's surface. As a result, the engine's strength (capillary force), is determined by the geometry discovered by the advancing interface [84]. The maximum amount increased up to 100 µL due to the increased size of the test zones obtained by the paraffin/beeswax dipping method. It was observed that the EVOLON® worked with the dipping method could hold up to 4 times more liquid than chromatography paper. Fluid confinement is improved in threads, and less fluid is lost unused in the fibers [85]. System modeling is required based on wettability design to understand fluid mechanics [86].

4. Conclusion

In this study, we tried to reveal the strengths and weaknesses of the production techniques and the resulting microfluidic platforms as summarized in Table 2. Patterning paper with PDMS, white glue, AKD, beeswax, and paraffin is much more flexible and simpler than photoresist. Resolution and cost are two of the most important criteria for evaluating the µPAD fabrication process [73]. When compared to the drawing method itself, it was seen that more durable barriers were created with glue, which is a cheaper material compared to other materials we use. Although the method could be applied with a cheap and easily accessible material, the channel resolutions were very low. Inkjet printing provides more control over the pattern because of the deposition technique. However, AKD required the use of heptane, an organic solvent. The printing technique, which enables the production of many different geometries at once, has a high resolution, but its resistance to solvents and reagents needs to be increased. It may be necessary to work with different hydrophobic materials in this regard. In this study, water-soluble white glue was tested using the printing method, but production was halted due to nozzle clogging. Methods that can produce higher resolution with glue can be investigated.

Simplicity allows scientists with limited experience in device fabrication to begin independent experimentation and adaptation of µPADs and µTADs. Detailed research into capillary wicking could help improve device design and suggest new capabilities. The development of new methods of manufacturing will expand their capabilities [87]. The cost of a microfluidic device is also important, and it should be as low as possible, especially if it is intended to be used in resource-limited settings. It is possible to achieve such cost savings by using inexpensive materials in conjunction with a cost-effective manufacturing process for mass production of microfluidic devices [56]. Minimizing the number of chemical solvents lowers manufacturing costs, particularly with the beeswax and paraffin patterned method we described here. It takes about 20-25 minutes to complete the process. Beeswax or paraffin pellets, a beaker, and heating equipment are all inexpensive and widely available. This kind of fabrication method is quite appealing to implement in laboratories with limited resources.

Surface properties of materials are among the most important features that should be evaluated during the production stages [88]. As an alternative to the filter paper used in this study, chromatography papers with different fiber thicknesses and pore structures should also be evaluated for the purpose. Thread types with designable fiber properties can provide different flow patterns and adjustable wettability. Studies can be continued with different papers and threads for the purpose.

By determining the working zones/channels on the paper/thread specific steps of a clinical analysis can be performed, such as sampling, pretreatment, and chemical reactions [89]. Paper and thread-based microfluidic platforms developed in this study can be used in many fields where analytical tests are used. Polymers and polymer-based composites are increasingly used structurally in many industries [90,91]. Various additives and fillers can be used depending on the desired physical data in the field of use as the final product [92]. Creating controllable, high-mechanical composite surfaces with nanomaterials [93] will help researchers in this field develop new perspectives. Natural threads, such as cotton, have superior tangible and synthetic properties in terms of water absorption and stability [94] may be a sustainable alternative. Further research is required to integrate paper and thread-based microfluidics with portable and low-cost platforms. Different channel/test zone geometries can be produced for specific purposes.

Direct methods are simple and ideal for rapid prototyping, whereas the use of intermediaries by indirect methods allows their adaptation in mass production [95]. Other microchannel fabrication methods exist that reduce fabrication cost and complexity, allowing the research community greater access to microfluidics [96]. Studies need to be continued to improve the disadvantages caused by the materials used and to discover a simple, cheap, and high-resolution method that can be accepted universally.

The fabricated microfluidic platforms can be functionalized and used in many areas where analytical tests are applied. Studies on diversifying channel geometries and increasing resolution need to be continued. It should be investigated which devices can be used to obtain qualitative and quantitative results. To make simple and cheap production techniques suitable for mass production, studies should be carried out from different branches.

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Table 2. Advantages and disadvantages experienced during work.

Fabrication method	Equipment	Hydrophobic Material	Solvents	Experienced advantages	Experienced disadvantages
Drawing	Ballpoint pen	PDMS White glue	Hexane DI water	Easy and flexible fabrication Easy access to pen and white glue Low cost for pen and white glue The water solubility of white glue Solvent resistance of white glue walls	Poor reproducibility Poor resolution Difficult access to PDMS and its curing agent Organic solvent needs for PDMS Multiple-step procedure Need for heat and UV treatment Cost of heat and UV treatment equipment Requirement of drawing on the double side to prevent leakage The low solvent resistance of PDMS walls
Inkjet Printing	Inkjet printer	AKD	n-Heptane	Easy and rapid fabrication High reproducibility High resolution Possibility of production of different channel designs Obtaining thinner channels compared to other tried methods in the study Low cost of AKD Possibility to work with lower sample/reagent/solvent volumes due to channel structures	Cost of printer Need for organic solvent and heat Multiple-step procedure The necessity of adjusting viscosity and concentration in a printable hydrophobic material
Plasma treatment	Plasma cleaner	AKD	n-Heptane	Easy fabrication Low cost of AKD	Need for plasma equipment High cost and accessibility of plasma equipment Customized masks are required for high-resolution plasma patterning Need for organic solvent and heat Multiple-step procedure
Dipping	Heater	Paraffin Beeswax	-	Easy fabrication One step procedure Low cost of paraffin, beeswax, and heater No solvent need High organic solvent resistance of patterned walls Applicable to both paper and thread	Poor reproducibility Poor resolution Customized magnets are required for different channel geometries

Author contributions

Nagihan Okutan Arslan: Design, fabrication, analysis, interpretation, writing, and editing**. Raghied Mohammed Helmy Atta:** Design and fabrication via drawing, plasma etching, printing techniques, interpretation**. Levent Trabzon:** Conception, design, reviewing, editing

Conflicts of interest

The authors declare no conflicts of interest.

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