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DEVELOPMENT OF PAPER-BASED MICROFLUIDIC ANALYTICAL DEVICE (µPAD) FOR DETECTION OF SARS-COV-2

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ABSTRACT

Paper-based biosensors are highly preferred today as a self-operating microfluidic biosensor as a new generation biosensor due to its portability, low cost and simple fabrication. Biosensors known as paper-based microfluidic analytical devices (µPAD), which have been used in a wide range of point-of-care analysis (Point-Of-Care-POC) applications in recent years, have begun to replace traditional diagnostic devices, especially in biomedical applications. Today, there are many different methods for the production of µPADs such as photolithography, inkjet printing, wax printing, paper cutting, plotting and plasma treatment. As an alternative to all these production methods, a new fabrication method has been developed for paper-based microfluidic devices created with toner using a laser printer. Washburn test was performed to examine the capillary flow performance of hydrophilic channels created on paper with the help of toner. In addition, the wettability of hydrophobic barriers created with toner was determined by measuring the water contact angle. In order to test the success of the created system, the detection of a new type of coronavirus (SARS-CoV-2) has been tested on the system. Since the fabrication of the developed system is made with the toner used in laser printers, it is one of the lowest cost and most accessible methods performed until now, and it has a commercial product potential that can be used in the diagnosis of many diseases.

KEYWORDS:
Paper-based microfluidic analytical devices (µPADs), biosensor, toner test kit, SARS-CoV-2, COVID-19

INTRODUCTION

Most diseases in developing and underdeveloped countries cannot be treated and remain untreated because they cannot be diagnosed. In order to detect the disease, expensive laboratory equipment and healthcare personnel who can use these devices are required. In addition, diseases cannot be intervened early because the procedures for detecting the disease take a long time [1, 2]. The World Health Organization, with the abbreviation ASSURED, has established various principles for the development of diagnostic tests suitable for Point-Of-Care-Testing-POCT. The main principles are; it should be cheap, sensitive, user-friendly, fast and robust, without having any equipment and can be easily delivered to end users.

These tests allow rapid and low-cost diagnosis of diseases in places with limited means [3, 4].

Paper-based microfluidic analytical devices (µPADs) are among the low-cost POCT tests of rapid quantitative measurements of various analytes. µPADs are paper-based biosensors that create hydrophobic barriers on the paper surface with various fabrication techniques, allowing a small amount of analyte to move along the hydrophilic channel with capillary force on the paper to obtain colorimetric results [5]. It provides biochemical determinations to give fast and effective results. While polymer-based microfluidic devices (PDMS) need to apply an extra external force for the liquid to flow, µPADs perform the fluid flow thanks to the capillary flow force without being dependent on an extra external force [6]. First developed by the Whitesides group at Harvard University in 2007, paper-based microfluidic Analytical Devices (µPADs), dip bar, with the simplicity and cost functions of the test lab-on-a-chip (LOC) device combined with the complex structure of lab-on-paper (LOP) as a new technology provides [1, 7, 8]. µPADs are more advantageous in terms of cost and simplicity, since they are not produced by combining more than one paper, such as lateral flow tests (LFT), but only one piece of paper [9].

A wide variety of µPAD fabrication techniques have been reported in the literature. Some of those; wax printing [10], inkjet printing [11], photolithography [12, 13], plasma processing [14, 15], paper cutting [16-18], laser processing [19]. The wax printing method is one of the most used methods due to its advantages such as fast, minimum device requirement and ease of application [20]. This method aims to create hydrophobic channels by printing wax on a hydrophilic paper surface using a wax printer.

In order for the hydrophobic channels created by printing wax to pass to the back surface of the paper, it is generally heated between 130- 150 ° C on the heating plate [8, 20-22].

The wax printing method is one of the most standard ways to produce µPAD designs. However, since the wax printer is both expensive and difficult to access, alternative production methods of µPADs are being investigated. As an alternative to the wax printing production method, laser printers have been used. The µPAD model, which is drawn on the paper surface with the help of design programs in advance, can be produced by printing toner using any laser printer.

The building materials of toner are generally composed of various polymers such as styrene acrylates and polyesters. In order for the toner printed on the paper surface to pass to the back surface of the paper and form hydrophobic barriers, it must be kept on the heater plate surface longer, unlike the wax method [23].

Covid-19 is an accessible disease that first appeared in Wuhan, China in 2019, causing an acute respiratory infection and causing an epidemic worldwide [24, 25]. In order to prevent the spread of the virus, it is very important to test as many people as possible and to monitor those who are affected. Clinical, research and public health laboratories have used various detection methods to detect the coronavirus [25].

There are two basic methods of detecting the virus. These; molecular and serological methods. Serological methods are used to detect past and present SARS-CoV-2 infection. These methods can detect the presence of IgG, IgM and IgA antibodies in the serum and plasma of a covid-19 patient [26].

In this study, it is aimed to produce µPAD by using the technique of printing toner on the paper surface of the µPAD system, which has been designed, as an alternative to other fabrication methods. In addition, it is aimed to determine the most optimal design by using different design models and to add innovation to the field of diagnostics by using a faster, easier and cheaper way of production with less samples compared to other diagnostic methods. At the same time, it is aimed to prove the successful workability of the system by ensuring that the reagents that give successful results when used in the lateral flow method for the diagnosis of SARS-CoV-2 are used in the µPAD system produced by the newly developed fabrication method.

MATERIALS AND METHODS

Materials for Covid-19 Antibody Detection. Mouse anti-human IgG, anti- Chicken IgY which use for capture protein, COVID-19 N Antigen, COVID-19 S1, RBD Antigen and Chicken- IgY which use for conjugation, Gold nanoparticles (AuNPs) with particle sizes of 40 nm, conjugate buffer were purchased from Shenzhen Aıvd Bıotech Inc. The phosphate buffered saline (PBS) was obtained from Biological Industries. Bovine serum albumin (BSA) were obtained from Serva Electrophoresis GmbH. Potassium carbonate (K_2CO_3) and sucrose were purchased from Merck. The blood and inactivated serum samples of Covid-19 patients were supplied by volunteer individuals.

Materials for µPAD Fabrication. Whatman filter paper Grade 4 was purchased from GE Healthcare and coffee filter paper (Tchibo) were used as chromatographic paper for the µPAD designs. A laser printer (Develop, ineo + 227) and heater plate (Heidolph, MR 3001) were used to create hydrophobic barriers on the surface of the papers. ImageJ program was used to examine the hydrophobic properties of the produced µPAD systems. Green liquid food coloring was used for colorimetric analysis.

µPADs Design and Fabrication µPAD designs were made by using the CorelDRAW 2020 design program. A total of 10 different designs (Figure 2) have been developed for Whatman and coffee filter papers. By designing hydrophobic barriers of various sizes and thickness, the flow velocity of the liquid on the paper surface and the possibility of liquid leakage out of the system through hydrophilic channels were investigated. The most optimal design that can be used in diagnostic areas has been selected. The designed µPAD systems were printed with 600 dpi print resolution toner using the Develop ineo + 227 model laser printer. The µPAD systems were heated with a heating plate at 200 ° C for one hour, enabling the hydrophobic barriers to be activated and penetrate the back of the paper at the same time.

Thus, µPAD was produced with the desired properties and has been developed as an alternative method to other fabrication methods. The design and production stages of µPAD systems are shown in Figure 3.

Contact Angle Measurement of µPAD Systems. The contact angle gives information about the wettability or non-wettability properties of the solid surface in contact with water. The contact angle varies according to the shape of the drop on the solid surface [27]. Representation of contact angle as shown in the Figure 1. The angle value measured after the contact of hydrophobic barriers printed with toner on Whatman filter paper and coffee filter paper with 5 µL of distilled water and the wettability levels were analyzed and the paper with the highest hydrophobicity was determined. The angle between the paper surface and the water drop was determined using the imageJ program.

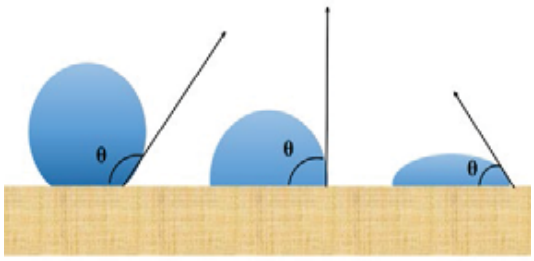

FIGURE 1
Representation of contact angle

Contact angle; If = 0 ° Superhydrophilic, Hydrophilic if 0 ° <θ 90 °, Hydrophobic if 90 ° <θ <150 °, Superhydrophobic if 150 ° <θ <180 °

Washburn Test of µPAD Systems. In paper-based diagnostic tests, the physical and chemical properties of their surfaces affect the test system. As the porous structure of the paper increases, the absorption of the liquid along the hydrophilic channel increases and helps the liquid to move forward thanks to the capillary force [28]. The paper type determined for the µPAD system changes the flow rate of the liquid along the hydrophilic path depending on the capillary force.

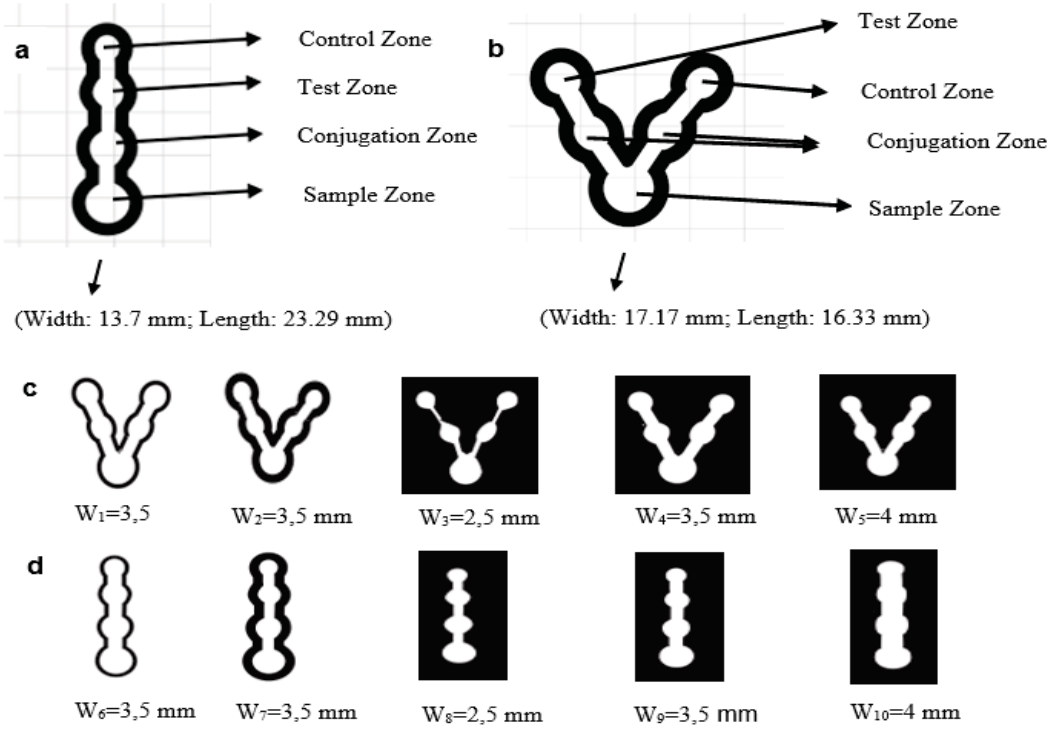

FIGURE 2
Schematic representation of the µPAD assay configuration and operational mechanism. a) Designs with two-way and b) one-way c) Design with different channel widths (W_1-W_5). d) Design with different channel widths (W_6-W_{10}).

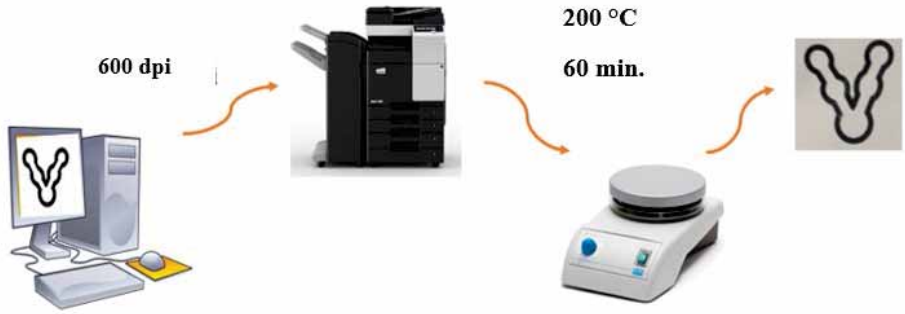

FIGURE 3
Design and fabrication stages of µPAD systems

According to the Lucas - Washburn equation, the distance the fluid travels varies according to the properties of the paper. The flow of fluid over the µPAD system; Factors such as hydrophilic channel width, average pore diameter, contact angle, fluid viscosity, surface tension change. Lucas-Washburn equation [29, 30];

$$L = \sqrt{\gamma D t / 4\mu} \quad (1)$$

L = distance the fluid moves, γ = effective surface tension of the fluid, D = average pore diameter,t = time, µ = fluid viscosity.

Hydrophilic channels designed in different lengths and diameters change the pace of the fluid. In addition, the most suitable design and the most suitable paper type were selected with the differences in the flow rate of the liquid between two different paper types with different pore sizes, with stopwatch and video recording.

Preparation of Gold Labeled Antigen Conjugates. To prepare the gold labeled antigen conjugates for N, RBD, S1 and Chicken-IgY; 8 µl,15 µl,16 µl and 8 µl of 0.2 M K2C03 was added into three different beakers, containing 1 ml colloidal gold (OD4), respectively, mixed for 2 min. Then, 10 µg, 10 µg, 25 µg and 10 µg of related proteins was added into N, RBD, S1, Chicken-IgY mixtures in order, mixed for 5 min. After this step, 10 µl of BSA or Casein Sodium Salt was added into each of mixture, mixed for 5 min. After mixing, the mixture was put into four different eppendorf and was centrifuged at 4500 g for 10 minutes at room temperature, then the supernatant was discarded from related tubes. 100 µl of conjugate buffer was added to Gold Labeled Antigen Conjugates (the AuNP conjugate) to be thawed.

The AuNP conjugates of N, RBD, S1 and Chicken Igy were mixed. The mixture was dispensed 4 µl on to membrane and dried at 37 degrees for 2h.

Preparation of Antigen Coated Mebranes. Mouse anti-human IgG and Rabbit anti-Chicken IgY were diluted to 1.5 mg/ml and 0.5 mg/ml, respectively, by using PBS and sucrose solution. After pipetting, the mixture was coated on to membrane to related regions (C and G) and dried at 37 degrees for 2h.

Detection Result of SARS-CoV-2 Using µPAD. Two different conjugation solutions were prepared for the test and control area and centrifuged at 13.500 rpm for 30 minutes. Then the supernatant was thrown and 100 µl of buffer was added to it and its color was optimized by pipetting. The reagents immobilized in the conjugation areas of the paper were left to dry in the oven at 37 ° C for 15 minutes. Positive sample was added to 30 µl sample area. After five minutes, the formation of a red color was observed as a result of binding of the conjugation solution with antibodies in the test area. The best result was observed after 10 minutes. This study has approved by Istanbul Yeni Yuzyil University ethics committee.

RESULTS AND DISCUSSION

Contact Angle Measurement Results of µPAD Systems. In order for the toner printed on both paper surfaces with a laser printer to become hydrophobic, it was kept in the heater plate at 200 °C for 60 minutes and it was provided to penetrate the back surface of the paper.

In order to analyze the wettability of the hydrophobic barriers formed, 5 µl of distilled water was dropped with a pipettor. ImageJ program was used to measure the contact angle. According to the analysis results, 104,5 ° contact angle of Whatman No: 4 paper and 106 ° of coffee filter paper were measured. Both papers were found to have similar hydrophobicity properties. Thus, it was determined that the fabrication method used was successful by observing the formation of sufficient hydrophobic barriers after the toner was heated. The measurement of the contact angles of the papers is shown in Figure 4.

Washburn Test Results of µPAD Systems. Washburn test was performed for selecting the most suitable µPAD design and paper type for diagnostic test applications. For each µPAD system produced for the test, 10 µl of green liquid was dropped and the speed of travel along the hydrophilic channel was measured by holding a stopwatch. It is as shown in the Figure 5 the µPAD front and back images produced.

According to the graph shown in Figure 6; the µPAD systems produced with Whatman No.4 paper have the same design and show the path of the liquid applied in different channel widths over time. The liquid in the µPAD system with a channel width of 4 mm (W_5) completed the system in approximately 17 seconds. However, the 2.5 mm (W_3) wide channel could only complete the system in 131 seconds.

According to the graphic shown in Figure 7, it shows the path taken by the liquid dropped on the µPAD systems, which is made up of the same design but different types of paper and prepared by applying the same production methods. The liquid in the µPAD system made of Whatman No.4 filter paper completed the system twice as fast as that produced from coffee filter paper. According to the measurements and tests carried out, it was determined that the liquid completed the µPAD system faster because Whatman No.4 filter paper has a stronger suction power than coffee filter paper. In addition, it has been observed that as the width of the hydrophilic channel increases, the velocity of the liquid in the system increases.

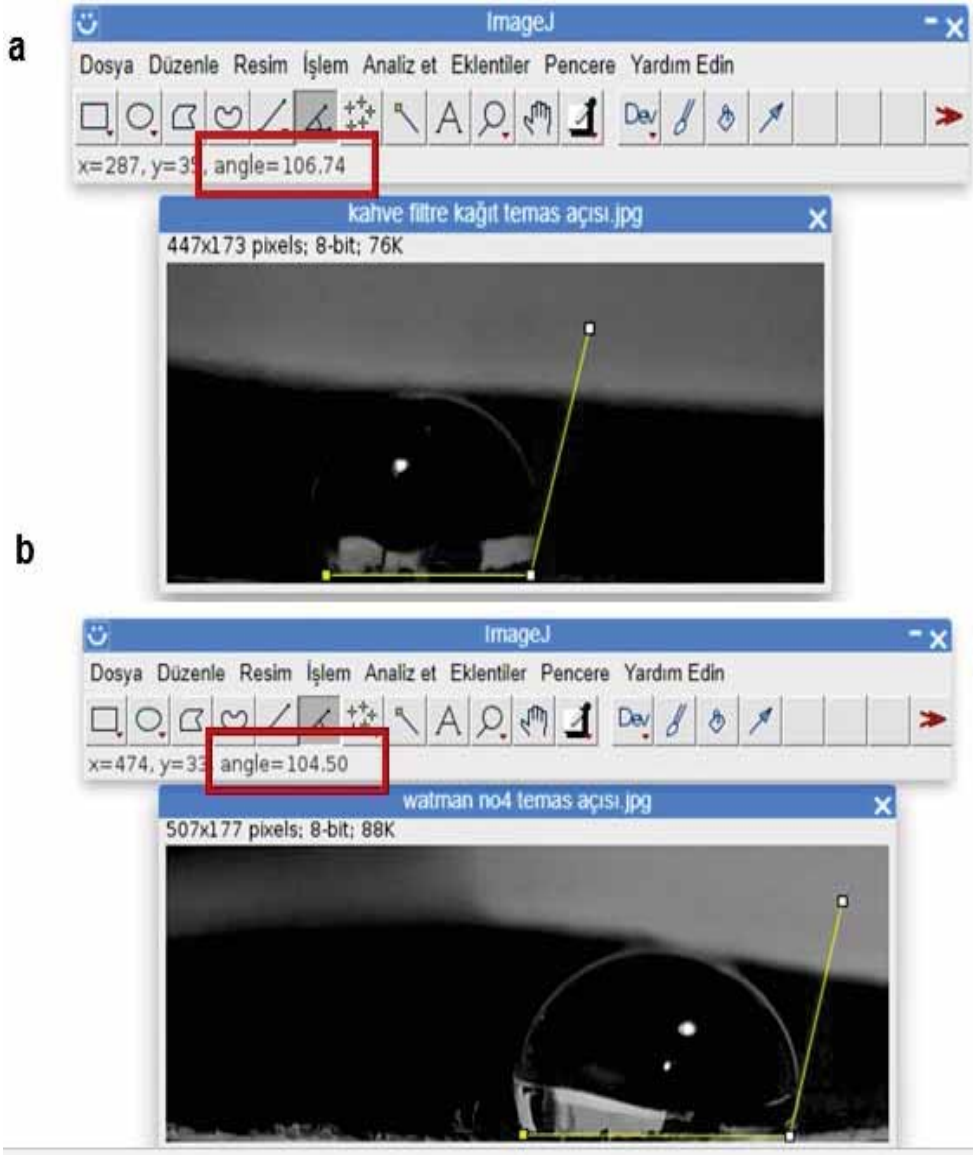

FIGURE 4
Contact angle measurement results a) Coffee filter paper contact angle b) Whatman No.4 contact angle

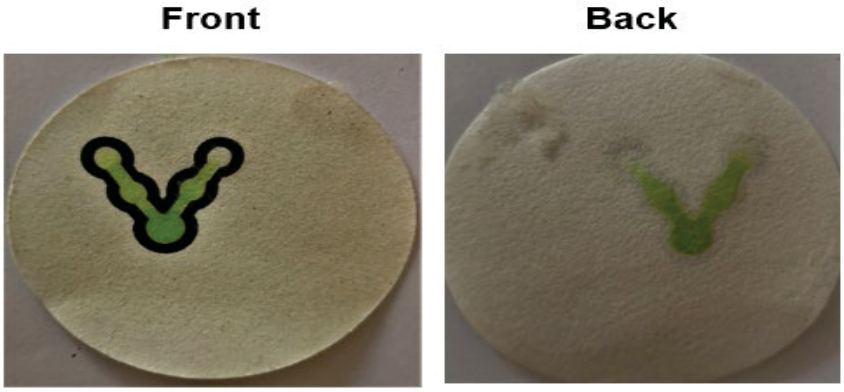

FIGURE 5
µPAD front and back images produced

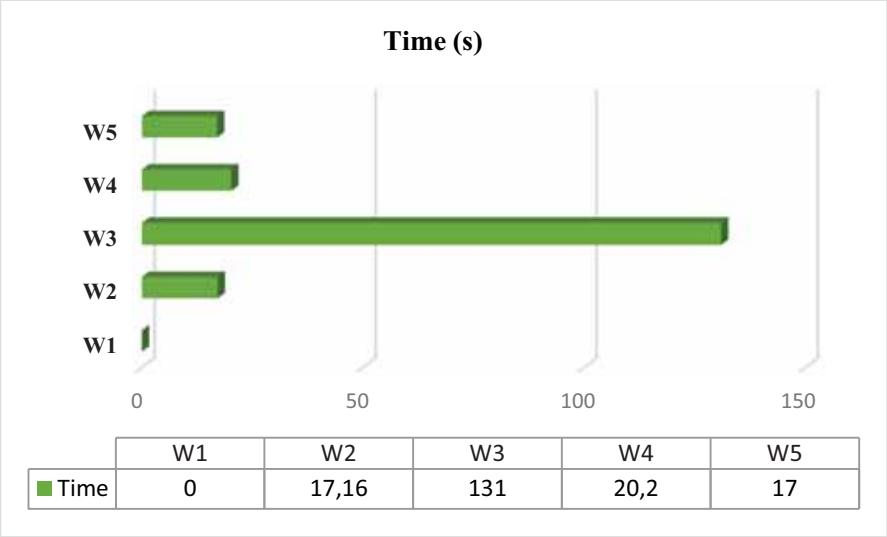

FIGURE 6
Washburn test results of µPAD systems. Time graph of designs with two-way and different channel widths (W_1-W_5) (Whatman No.4)

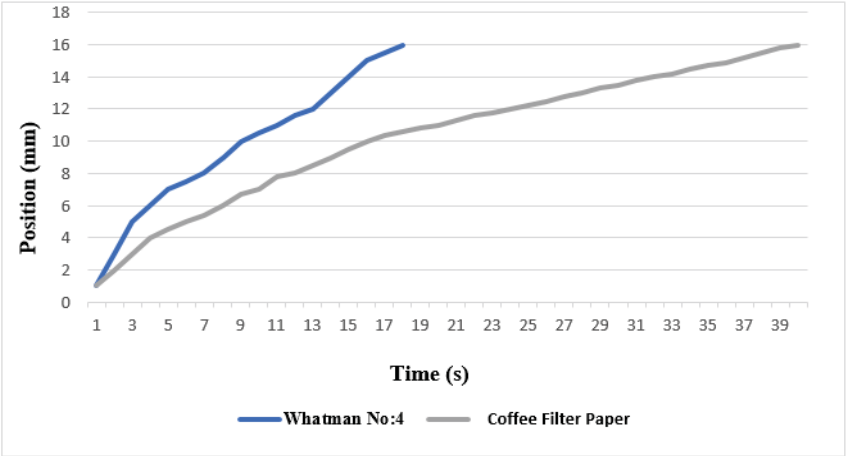

FIGURE 7
Position-time graph of µPAD systems produced from two different types of paper

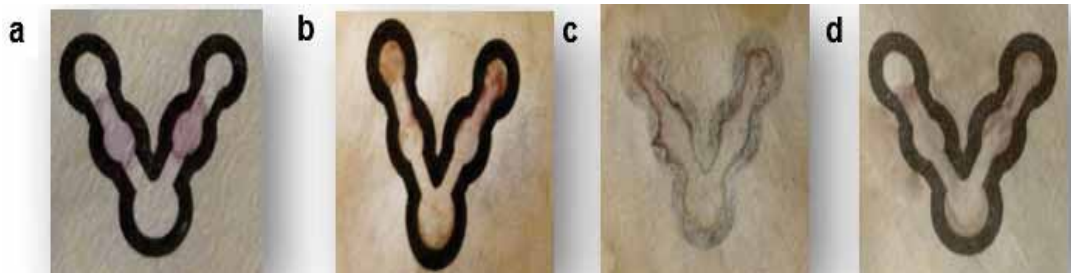

FIGURE 8
a) Ready for test µPAD b) Positive sample result front surface c) Positive sample result back surface d) Negative sample result

Detection result of SARS-CoV-2 using µPAD. The positive sample was pipetted 30 µl directly into the sample area. After five minutes, the formation of a red color was observed as a result of binding of the conjugation solution with antibodies in the test area. The best result was observed after 10 minutes. Colorimetric determination of the positive sample's results on the µPAD system, both in the test area and in the control area, was achieved. It was determined that the negative sample did not create color in the test area, but the control area was positive as proof that the kit system was working validly.

Figure 8a, kit ready for μPAD testing. Colorimetric determination of the positive sample's results on the μPAD system both in the test area and in the control area was achieved (Figure 8b). Positive sample result back surface as shown in the Figure 8c. It was determined that the negative sample did not produce color in the test area, but the control area was positive as proof that the kit system was working validly (Figure 8d).

It is known that the Whitesides group at Harvard University developed the μPAD system, which was cheap, easily accessible, fast and sensitive, used primarily in biomedical fields and introduced to the whole world, as an alternative to expensive and long-lasting laboratory tests [1]. There are many fabrication methods of the μPAD system. The main ones are; photolithography, inkjet printing, wax printing, paper cutting, plotting and plasma processing [31]. Unlike other methods, hydrophobic patterns were obtained by using a laser printer with the help of toner, as suggested in the literature, as it has easier, cheaper and faster fabrication features [23].

The study consisted of three steps. In the first step, the μPAD system, which will be used for SARS-CoV-2 detection, has been designed. In the second step, heating processes have been carried out on the hot plate so that the patterns printed on the paper show hydrophobic properties. Washburn tests and contact angle measurements have been made and preliminary optimization of the system was carried out for biomedical diagnosis. Preparation of the reagents to be used in the third step and optimization of the conjugation solutions have been carried out.

In the first step of the study, the patterns designed with the CrolDRAW program on the papers have been printed with a laser printer. In order for the printed patterns to be hydrophobic, they have been heated on a hot plate at 200 °C for one hour. As the polyester-based resin has been formed, the toner content melted and penetrated the back surface of the paper, thus creating hydrophobic barriers.

In the second step of the study, contact angle measurements and washburn experiments have been performed. According to the contact angle measurements, the contact angle of the Whatman No.4 filter paper was 104.5° and the contact angle of the coffee filter paper was 106°. In the literature, the contact angle of the patterns obtained with toner on whatman No.1 paper using a laser printer was measured as 120.8° [23]. In another study, the contact angle of the hydrophobic barriers created using a 3D wax printer has been measured as 104° [32].

In the literature, it has been stated that biosensors with different channel widths can change the speed of the liquid on the paper. It has been shown that the fluid progresses the fastest on the channel with the largest width among the patterns with channel widths of 1.2 mm, 1.6 mm and 2 mm, respectively [22]. In this study, Wasburn test has been performed on Whatman No.4 and coffee filter papers. Patterns with hydrophilic channel widths of 2.5 mm, 3.5 mm and 4 mm, respectively, have been designed.

In the pattern with a channel width of 2.5 mm, it has been determined that the liquid moves more slowly than the others. In addition, it has been determined that as the thickness of the hydrophobic barriers printed with toner increases, the probability of the liquid overflowing from the channels decreases.

The velocities of the liquids moving along the hydrophilic channel with the capillary flow force on the paper surface have been compared. It has been determined that the liquid moves twice as fast as the coffee filter paper because whatman paper absorbs the liquid faster due to its porous structure.

When evaluated in terms of cost, diagnostic kits produced with the lateral flow technique are created by systematically combining three different papers. In addition, the amount of reagents immobilized on paper and the sample used are less than lateral flow test systems. The developed system provides more advantages than other methods in terms of both the amount of reagent used and the faster results of the system.

CONCLUSIONS

We have demonstrated paper-based microfluidic diagnostic devices that can be an alternative to traditional laboratory devices, are fast, low-cost, simple to manufacture and easy to access. Since the fabrication of the system developed within the scope of this study is made with the toner used in laser printers, it is seen that it is one of the lowest and most accessible methods realized so far. In order to make diagnosis more practical in underdeveloped and developing countries, the production of low-cost, easily fabricated paper-based microfluidic kit was made with toner using a laser printer. The paper-based device developed within the scope of the study has a commercial product potential that can be used in the diagnosis of many diseases quickly without the need for laboratory personnel and medical equipment. In future studies, it is planned to continue the studies by projecting this system in order to optimize it and to use it in different disease diagnosis.

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Authors' Contribution. SCA and RD designed, performed and analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

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